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ANNALS OF
INTERNAL MEDICINE

VOLUME 21 JULY, 1944 NUMBER 1

THE GREAT NEED FOR INTERNISTS IN THE NAVAL MEDICAL PROGRAM *

By Ross T. McINTIRE, Vice Admiral, Medical Corps, U.S.N., F.A.C.P.,
The Surgeon General of the Navy

OUR outstanding President, Dr. Paullin, has given so much to the war effort that I want to take this opportunity to express to him the thanks and appreciation of the Navy for the splendid work he has done. In addition to his being President of our College, and President of the American Medical Association, he has assumed an added responsibility as Honorary Consultant to the Secretary of the Navy and the Surgeon General of the Navy. I can assure you that as he relinquishes the details of the two positions which he now holds in civil medicine, we in the Naval Service will call upon him for all the time he can reasonably give, and you, knowing him, can imagine what that will be.

I think I should tell you at this time just what this small group of Honorary Consultants do for the Medical Department of the Navy. They have been perfectly unselfish in the time they have given. I have sent them over all parts of the Continental United States, and even overseas, where they have inspected our various medical facilities, bringing back to me complete reports on how our activities are functioning. We have our over-all medical inspectors, men of ability and long experience in naval affairs, but these men from civil life bring a new viewpoint which has proved tremendously valuable. We expect to continue to use them throughout this war and I can assure you that they are helping immeasurably in the achievement of greater efficiency.

It must be extremely satisfying to the members of the College to see the great strides that have been made in scientific medicine in these past two years. Extremely satisfying, because you have all had a part in it. As far as medicine is concerned, this war effort is being prosecuted not only by the men in the Service, but because of the wise use that is being made by the

* Presented by Rear Admiral Luther Sheldon, Jr., Medical Corps, U.S.N., at the Scientific War Session, American College of Physicians, Palmer House, Chicago, Illinois, April 1, 1944.

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Army and the Navy of key people in civil life, it becomes a joint effort. Consider, too, that the Medical Departments of the Army and the Navy are made up with a tremendous majority of Reserve Officers. In fact, out of 11,000 officers in the Navy, 9500 of them are Reserve Officers.

There is one disturbing factor, however, that has come to the fore, and only recently so—it is the fact that we do not have a sufficient number of internists in the Service. A few years ago the reverse was true. I will use an illustration to show you why that is true. In our early work in the South Pacific, sanitary and tropical disease control was very difficult of accomplishment. This was due, in the main, to the lack of competent, trained men to put our plans into operation. When the Seabee battalions were formed, it was arranged for a certain number of men in each battalion to be especially trained in sanitary engineering and malaria control. Thus, we made rapid strides in cutting down the incidence of certain tropical diseases. As the tempo of the war picked up, however, the spectacular side came quickly to the fore, such as construction of airports, aiding in the landing of troops on beachheads and, in fact, taking a rather active part in the combat necessary to secure a foothold on the beaches. What happened? When we wished to set up a Mobile Hospital, or put in some drainage ditches to make a camp-site livable, these men were not to be found, because they preferred the spectacular work with the combat troops. So it is with the man who does internal medicine. He is not in the spectacular side of the field. In other words, the young man in medicine wishes to be a surgeon. He wants to do traumatic surgery—orthopedic surgery—plastic surgery—for this type of work takes him into the foreground of war activity and the man of internal medicine does his hard plugging unseen.

As I have said many times before, it will never do for us to over-specialize in the Naval Service. Surely, in time of war, it is necessary to have a rotating service so that the internist can have his chance at first aid stations and at advance base hospitals. Although the surgeon can not go into a ward and handle the cardiacs that come through, or the chronic nephritics and other difficult cases, still this man must be taught to handle acute medicine. He must know what to do about the acute respiratory diseases and he must also know what to do when he has cases of exacerbation.

We have been extremely fortunate in the Navy to be able to use our specialists in the jobs they are best equipped to handle. By actual count, we find that we have employed 72 per cent of our medical officers in the specialties in which they are trained.

A short time ago I had an opportunity to spend a great deal of time on one of our very large ships. In fact, it is one of the most modern we have. During those few weeks I was able to spend much time with our medical personnel and here I had the extreme pleasure of seeing well-trained surgeons and well-trained internists working together as a splendid team. I saw a highly trained cardiologist do a very difficult gangrenous appendix. I saw an excellent eye, ear, nose and throat man make a diagnosis on a complicated

chest condition. Here, we have men who were on their toes vying with one another to see what could be done to improve the medical service of that ship.

We have a great responsibility today to make a determination on what should be done about specialization of medicine in this country and how we should best go about doing it. I think we should give serious thought to what has happened in the past and find ways and means to prevent it from happening again, should we be forced into another war in the next twenty years.

Medical education is in a peculiarly critical period. We have a wonderful opportunity to lay down a basis for sound teaching in the pre-medical field, and in medical education itself, that should endure over a long period of time. I believe it is up to this organization to step in and take a very definite, leading part in this determination. The pre-medical field requires fully as much attention, if not more than the medical courses.

One thing I should like to call to your attention is that in our opinion visual instruction has come to stay, and in medicine it will take its place in a most decided fashion. How, then, can we best be prepared to institute this even in the days of war? There is a considerable amount of work being done, but it is rather sporadic. I can tell you that the Navy is actively at work in this field. We have teams of highly trained technicians, headed by doctors, that are in the combat zones doing a great deal of photographic work which will be prepared for teaching purposes. We are establishing photographic units in all our large hospitals, which will record for all time the technic of our various departments. Now, again, the surgical sections have a great advantage, for here the anatomical side comes in and the spectacular is there. So, I must turn to you for assistance as to methods of working out successful teaching films in internal medicine. These must be made attractive for the medical student will not tolerate dullness. We have some ideas and we have been following them. In the tropical diseases we have no such problem and we are coming up with some exceedingly interesting work. We expect to make all of this material available to teaching institutions in civil life. Very naturally, we expect to use them in our schools. I am asking you today to give thought to this in your deliberations, going well beyond what you have done in the past.

Turning now to the medical problems that we are facing, our first and foremost continues to be malaria. In this past year we had many thousands of original admissions in this disease. I do not have to tell you what that means to combat troops. We are making rapid strides in malaria control, but that is not the answer. Immunity in malaria is the thing for which we are striving.

Filariasis is a problem that will dog us for months and months to come, while we are struggling for the solution. We do have the answer to other tropical diseases and they are being handled successfully. Much is being done to develop therapy that will shorten the time on the sick list for many of the dysenteries. We expect to see results even in filariasis. Our great

trouble here is the handling of these men, for you all know that in the early stages of this disease symptoms come—then there is a period of remission during which time the patient feels quite well—following that fresh exacerbations occur from time to time and the patient who has seen the horrible end results of this disease among the Polynesians pictures himself in their plight. Thus we have a psychological problem with which to deal that can easily become psychoneurotic. Therefore, there is great need for speed in finding ways and means to handle this condition, for we have many thousands of cases.

We will continue to go on doing experimental research in all the tropical diseases with the expectation that we will find the answers to the troublesome questions that have faced medical men over such a long period of time. In other words, we will try to find the conclusive answers to the preliminary studies of such men as Manson, Strong, and Stitt.

I believe that you will be interested to know just what we have done in the field in these past two years in the way of handling our patient load. Our Hospital Program, for work beyond the continental limits, was developed with the sure knowledge that practically all these hospital facilities would be placed among the various islands of the Pacific. Our hospital units were developed so that they could subsist themselves if necessary. I am glad to tell you today that we have hospital units of 100 bed capacity and of 2,000 bed capacity, all in a more or less mobile state. I say "more or less" because these tremendous institutions are mobile up to the time we set them down. Then, of course, as the months go along and they have been in active use in their theaters, it is a real problem to tear up the buildings and move them to another site. In some instances, when we need to move a large hospital facility two thousand (2,000) miles, from the back area to the forward area, we find it more economical to set up new buildings and we simply move up the equipment.

A Unit has every modern facility that a hospital in the continental limits has. It is capable of furnishing its own electrical supply for it has a modern power plant. It has a water purification system that really works. It carries a modern laundry. Its galley equipment is a thing of beauty. The laboratory facilities are complete in every detail. The roentgen-ray equipment was designed with the help of the best engineers in this country. The workshops are air conditioned, and that has proved a great blessing to the patients and to the doctors. In many of our institutions we have at least one ward that is air conditioned so that the critically ill patients may have the benefit of it. So, you can see that we are able to do any kind of work that we are called upon to perform in these mobile units.

Since December 7, 1941, we have hospitalized over 208,000 patients in these various mobile units. The results, from such adequate hospital treatment, so close to our front lines, have paid us tremendous dividends. I can not give you the exact record of each hospital, but I can tell you that some of them have astonishing ones. One, especially, established a record

over a two year period of a mortality rate of less than 1.5 per cent. This hospital handled a majority of the battle casualties which occurred on Guadalcanal.

You might say that we are carrying on too elaborate a program, but I can not agree with this for I see no reason at all why we should spend billions of dollars to kill our enemies and only a few hundred thousands to save the lives of our men. I have no feeling whatsoever about asking for a reasonable amount of money for the hospitalization of the sick and the wounded. I am telling you all this for I want you to know just how far we have progressed in providing modern hospitalization for our men close to the battle lines.

These hospitals are made doubly useful by the use of air transportation. We have reached a point where we are now insisting that mobile hospitals be located as close to flying fields as possible, so that the patients will not have to be juggled over rough roads in transit from the field to our institutions. It will be a marvelous thing when we can do away with all forms of ambulance transportation by land, for here we have one of the greatest instruments for producing—or let me say increasing—shock.

The internist who is fortunate enough to be assigned to one of these mobile hospitals will be practicing medicine at a frontier and yet he will have every modern facility that he has in his own hospital at home. He will be the master of his own division and he will have the great satisfaction of being able to practice his specialty among the battle casualties that are efficiently moved into his hospital, where his knowledge, built up on years of experience, will be invaluable to the surgeon who will be called upon to treat the injured.

Now, I want to say a word about our Hospital Ships. I speak with a certain amount of feeling about these ships for I spent over five years of my service in such duty. I can tell you that there is no more satisfying place to practice medicine, for here you find a group of men living together, isolated, entirely dependent upon themselves. These ships do a remarkable job, for they have two duties to perform—they serve as a means of evacuation for the wounded and they receive and care for the casualties as they occur in the Fleet.

Here, again, we provide the most modern equipment that is known. The internist who is head of his department on one of these ships will have every known means, in a mechanical way, to improve the handling of his patients. These ships carry everything in the way of laboratory equipment. Their roentgen-ray plants are modern and they carry all of the luxury equipment with which we feel we must practice medicine today. In other words, a basal metabolism is a routine practice; the electrocardiograph has long been standard equipment—and I could go on and on.

On a Hospital Ship we practice medicine in a different fashion, for here every medical officer has an opportunity to see every critical case that comes on board. The internist becomes a fair surgeon; the surgeon learns again

something about internal medicine; and the ophthalmologist finds that there is such a thing as the practice of medicine. I can say this for I know something about that specialty. My only complaint is that our doctors in the isolated specialties, in civil life, are too busy to be able to see enough of medicine.

Perhaps, I may sound as though I am bragging about the practice of medicine in the Navy. I am not. I have simply been stating facts. I will be very glad to brag about the splendid way in which the Reserve Officers have stepped into the organizations which I have just described. As I have said earlier in my remarks, you should feel as proud as I do of your fellows who are serving with the Armed Services.

I suppose this war will bring about many new things that will be of great constructive value to medicine. I am perfectly sure, however, that the greatest thing it will bring about is the understanding that doctors will have among themselves. This war is not lasting just a few months; it is lasting over a period of years. I am of the firm conviction that we have several more years to go. Because of that fact men will learn the great value of close association in medical practice and I am hoping that out of this war will come sound opinions as to what we can do in civil medicine to have closer association among our doctors.

In closing I want to say a word about the necessity for postwar planning. Your outgoing President is performing a leading rôle in this. He realizes, as I do, that medicine must make a real contribution in these plans. We have seen many danger signs from people who are not qualified, but who are proposing plans for medicine. I am firmly convinced that plans must be made. We must find ways and means to provide medical and hospital care for the thousands of men and their families who will be attempting to find a place to live following this war. The shifting population that must settle down again will add to our difficulties. The doctor's fee is not a problem, for I feel very definitely that the good doctor still practices medicine and too often forgets his fee. We must find ways and means also to reduce the collateral costs of medical and hospital care. I hope the American College of Physicians will take a leading part in this and that it will clearly and unselfishly review the events which have led up to this necessity and offer sound and concrete suggestions.

DEMEROL: A NEW SYNTHETIC ANALGETIC, SPASMOLYTIC AND SEDATIVE AGENT. I. PHARMACOLOGIC STUDIES *

By Fredrick F. Yonkman, M.D., Paul H. Noth, M.D., M.S., and Hans H. Hecht, M.D., *Detroit, Michigan*

The disadvantages attending therapeutic use of morphine and other analgetics have impelled investigators in numerous fields of medical endeavor to seek an adequate substitute for the relief of pain. Codeine, dilaudid, snake venom and other agents recently introduced do not subscribe in every respect to the specification of 'adequate substitute' because of various side-effects or other disadvantages associated with each. However, a synthetic substance which in some respects equals or surpasses morphine is available in demerol. It appears in the literature under various names such as Dolantin, Dolantol, D–140, S–140, and more recently as Demerol, which is the most generally accepted term in this country.

We have studied the drug pharmacologically and clinically. The results of a clinical study of demerol as a morphine substitute both in acute and chronic conditions will be presented in a subsequent article. In this present report we wish to review briefly its chemical features and pharmacologic properties and to present the results of our animal and human studies of its effects on smooth muscle of the uterus and intestine. For a more detailed consideration of its general pharmacologic properties the reader is referred to the work of Schaumann [2] and Gruber, Hart and Gruber.[7]

Chemistry

Demerol was synthesized in 1939 by Eisleb and Schaumann [1] as the ethyl ester of 1-methyl-4-phenyl-piperidine-4-carboxylic acid. This is a white, insoluble crystalline substance which becomes soluble in water as the hydrochloride salt. In this paper, the term demerol implies the hydrochloride form. It is slightly bitter and is non-irritant to the gastrointestinal mucosa. At one time the carboxylic acid modification was of interest because of its peripheral or local anesthetizing potentialities, but in the ethyl ester form it attracted greater interest because of its analgetic and spasmolytic actions.

A study of the chemical formula proposed by Schaumann [2] indicates the relation of demerol to atropine and also to morphine. The latter has been commonly accepted as a derivative of phenanthrene, but Gulland and Robin-

* Received for publication July 10, 1943.
From the departments of Pharmacology and Therapeutics and of Medicine of Wayne University and from the department of Medicine of Receiving Hospital and the Medical Division of the William J. Seymour Hospital. This interdepartmental study of demerol hydrochloride received the support of Dr. J. Mark Hiebert of the Alba Pharmaceutical Division of the Winthrop Chemical Company, Inc. The project was aided by the A. Mendelson Memorial Fund of Detroit.

ATROPIN, DEMEROL (Dolantin), and MORPHINE
(Schaumann)

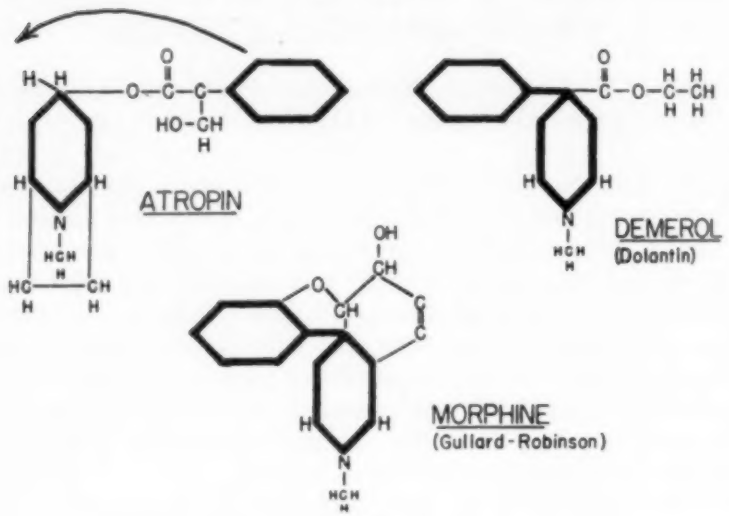

FIG. 1.

son [3] have proposed the piperidine formulation pictured in figure 1. If this be the true formula for morphine, not only is the chemical relation of demerol to morphine and atropine apparent but the atropine and morphine-like pharmacologic actions of demerol become easier to understand.

PHARMACOLOGY

General Actions. Demerol has been studied pharmacologically by several investigators [1, 2, 4, 5, 6, 7, 8, 9, 10] both in this country and in Europe. It resembles atropine in its anticholinergic action in the production of mydriasis, suppression of saliva, insulation of the heart, bronchi and intestine against vagal stimulation. It resembles papaverine in its spasmolytic action since it also directly relaxes the bronchi, intestine, uterus and blood vessels. Demerol resembles morphine in its capacities to produce analgesia, sedation, euphoria and, at times, side-effects somewhat similar to those produced by morphine.

Toxicity. Acute toxicity studies have been reported [7] in which the M.L.D. 50 of demerol was 221 mg. per kg. orally and 147 mg. per kg. intraperitoneally in white mice, but 93 mg. per kg. intraperitoneally in white rats. In rabbits, the intravenous M.L.D. 50 ranged between 20 and 32 mg. per kg. depending upon weight of the animals employed.

Chronic toxicity studies [7] showed that white mice tolerated 90 mg. per kg. daily by mouth for 25 days without manifesting any ill effects. Gruber also fed four dogs 50 mg. per kg. of demerol by mouth daily, six days a week

for five weeks. Salivation, some nausea, and rare vomiting, with definite evidence of distaste for the drug resulted after the first week. After five weeks Gruber increased the daily dose to 100 mg. per kg. Two dogs survived a total of 12 doses at the higher level and "at no time during the entire seven weeks was the blood picture of any animal significantly different from the control." Barlow [9] treated eight adult dogs with a daily dose of 75 mg. per kg. and 24 monkeys with 40 mg. per kg. daily for 10 months. "Although a slight degree of anorexia and a slight falling off in weight were observed no deleterious effect was produced with respect to the hematopoietic system nor upon necropsy were any histologic changes in liver, kidneys, spleen, gastric mucosa, or bone noted."

Acute and chronic toxicity studies in man are reported in the clinical paper.[11]

*Uterine Responses.** Isolated strips from guinea pigs, virgin and non-virgin, were studied in tissue baths ordinarily used for these experiments in which the muscle is bathed in Locke's solution, pH 7.5 to 7.6 at 39° C., and contracture changes are recorded on the kymograph. Figure 2 illustrates the typical results which were almost uniformly obtained in over 55 experi-

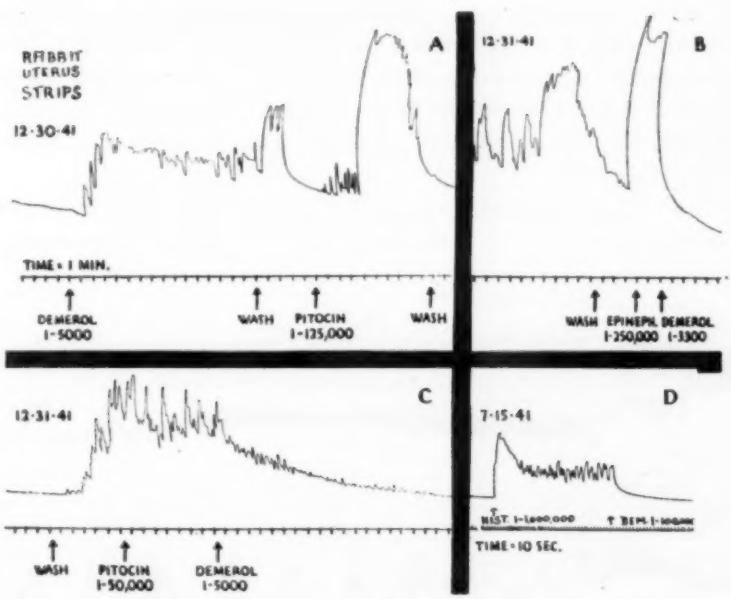

FIG. 2. Kymographic records of uterine strips of rabbits and their responses to:

A. Demerol, 1–5000 and pitocin, 1–125,000
B. Epinephrine, 1–250,000 and demerol, 1–3300
C. Pitocin 1–50,000 and demerol, 1–5000
D. Histamine, 1–1,000,000 and demerol, 1–100,000

Time = 10 minute intervals in A, B and C and 10 seconds in D.

* We are grateful to Dr. Marshall Purdy and Dr. Garnett Ice for their coöperation in these experiments.

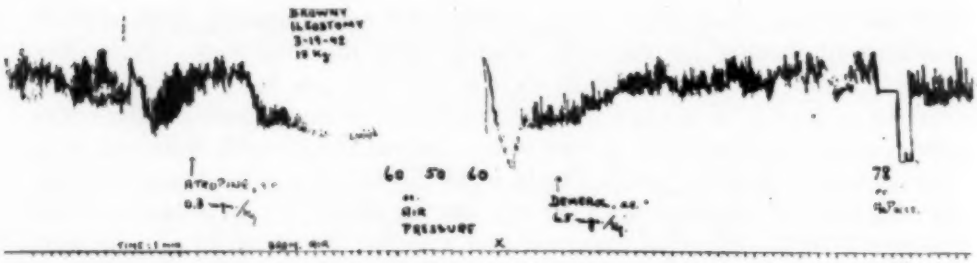

FIG. 3. Tracing of ileum of unanesthetized dog with balloon inserted through ileostomy. Atropine, 0.3 mg. per kg. subcutaneously, followed by demerol, 6.5 mg. per kg. subcutaneously. Figures 60, 50 and 60 indicate volume of air in c.c. required to elicit painful response to distension before demerol and 78 c.c. denotes average volume required to elicit similar response after demerol.

Time = 1 minute intervals.

ments. Demerol usually relaxed the segment which had previously been activated either by epinephrine, 1–1,000,000 to 1–250,000, pitocrin, 1–125,000 to 1–50,000, histamine, 1–10,000,000 to 1–1,000,000, barium chloride, 1–10,000 or physostigmine, 1–20,000. The degree of relaxation or inhibition depended upon the dose of stimulant as well as that of demerol. Demerol was an effective spasmolytic in a dose of 1–100,000 on a uterus under strong histamine stimulation as illustrated in figure 2, D. Frequently, but by no means consistently, demerol activated the flaccid, previously untreated uterine strip (figure 2, A). Our results amply confirm previous work [2, 7] in that the flaccid uterus may be stimulated, whereas relaxation usually ensues in the tonic or active segment.

Intestinal Responses. Balloon experiments, the technic of which has been described previously,[12] were conducted 12 times in four trained, un-

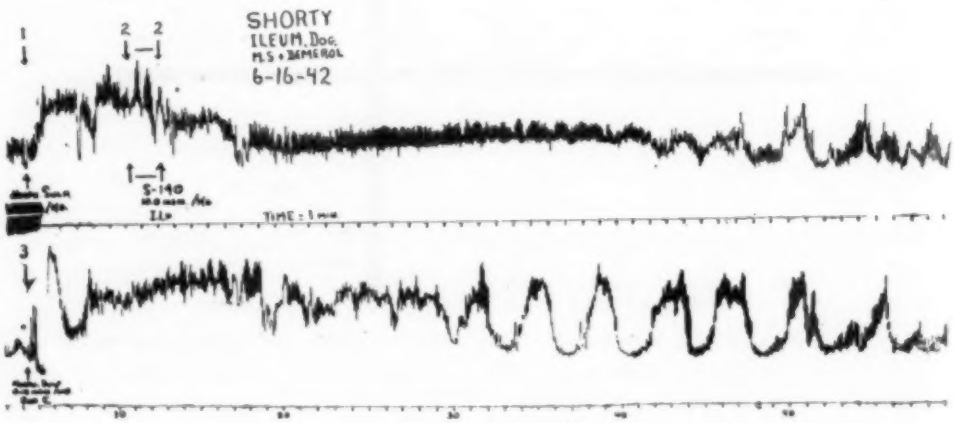

FIG. 4. Dog, unanesthetized, tracing of ileum. Drugs administered subcutaneously in following order: morphine sulphate, 0.1 mg. per kg., demerol (S–140) 10 mg. per kg., morphine sulphate, 0.1 mg. per kg.

Time = 1 minute intervals.

anesthetized dogs with ileostomies or with Thiry-Vella loops of ileum. Our experiences were similar to those of Gruber,[7] since the normal dog ileum was uniformly stimulated in tone, peristalsis and segmentation. These effects were evident even after atropine had rendered the intestine almost quiescent (figure 3). However, if morphine had first been administered to activate the intestine [12] as was the case in six experiments, even to the point of vomiting, demerol markedly depressed some phases of intestinal activity (figure 4) and especially segmentation (figure 5). These findings do not agree with those of Gruber who states [7] "As far as could be determined, this latter injection (Demerol) had no significant effect upon the morphine re-

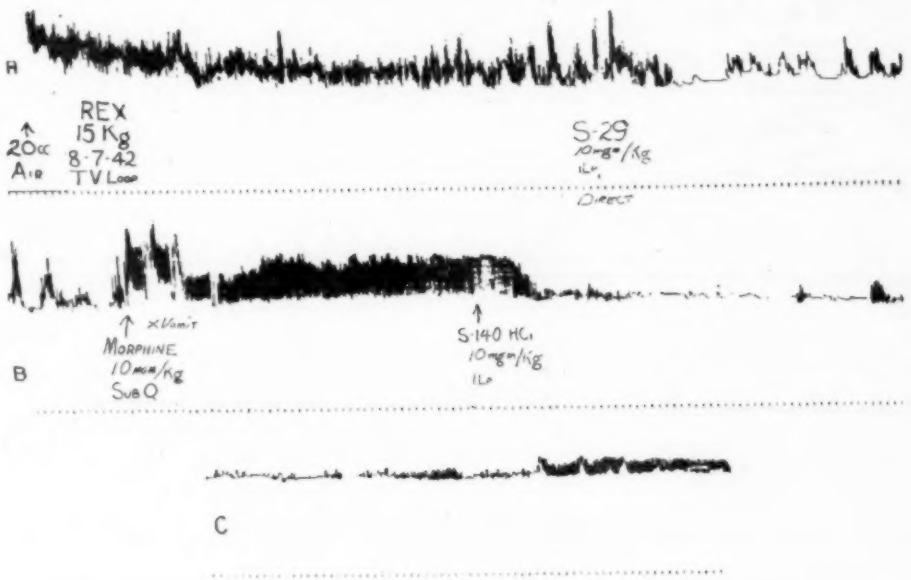

FIG. 5. Dog, unanesthetized, tracing of ileum. Drugs administered subcutaneously in following order (B): morphine sulphate, 1.0 mg. per kg., demerol (S–140), 10. mg. per kg. inserted through ileostomy. Recovery from relaxation approaches in C.
Time = 1 minute intervals.

sponse." We have not attempted to activate the intact intestine by any other agents, but it would be of value to study the tranquilizing effect of demerol after pituitrin, physostigmine or concentrated sodium chloride given intravenously.[13]

If the intestinal stimulating action of demerol in the dog should find its counterpart in the human intestine, the drug might be useful in the treatment of postoperative ileus and of diarrhea. Therefore, intestinal motility studies were conducted in patients * with ileostomies, cecostomies, colostomies or with the indwelling Miller-Abbott tube at various levels of the gastroin-

* We are grateful to Drs. R. Crowley, J. T. Downs, M. H. Blau, L. Whelan, J. Posch, B. N. Craver and R. Bauer for their coöperation in this phase of the work.

testinal tract. Intestinal contractions were registered against air distended balloons which were attached to catheters; these were in turn connected with a bromoform manometer whose float transmitted contraction waves against a smoked kymographic paper. Fifteen experiments were conducted on five patients and in only one instance was there evidence of stimulation after demerol. This occurred in one experiment on a patient who on four other occasions had no colonic stimulation after demerol. Figure 6 reveals that

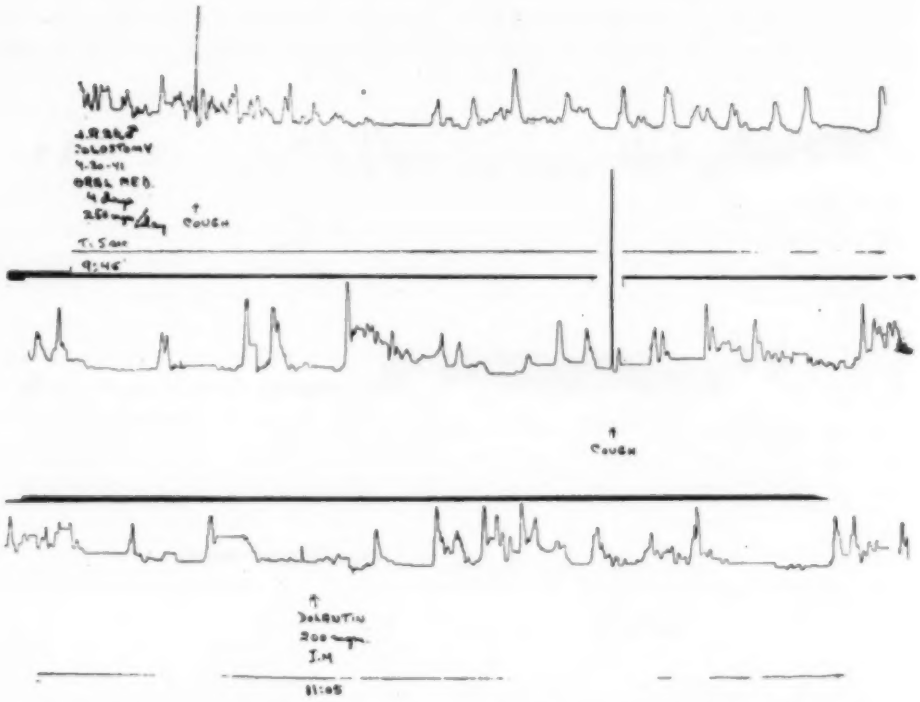

FIG. 6. Patient, H. R., age 26, colostomy. Tracing of colonic activity after patient had received 250 mg. of demerol orally for four days. No appreciable effect observed. Demerol (dolantin), 200 mg. intramuscularly likewise produced no significant change. Time = 5 second intervals.

daily oral medication with 250 mg. per day for four days followed by 200 mg. intramuscularly failed to alter the normal motility of his colon. This patient was of special interest because in two experiments demerol failed to check tone increase by morphine and even in large doses demerol interfered in no way whatever with his ward ambulations or daily habits.

The quiescent effect of demerol on the human ileum is observed in figure 7. Normal peristaltic frequencies were aborted for almost 40 minutes, after which morphine was capable of exerting its normal tone increasing or "splinting" effect upon the ileum.[12] The absence of kymographic evidence of intestinal stimulation was verified by the patients' persistent negation when

questioned concerning "cramp-like pain or colic" after demerol injections. This was not true in our morphine studies.[12]

In none of our experiments with demerol was there evidence of a lessened intestinal tone, save one, which developed gradually over a period of approximately one and one-half hours. What relaxing effect, if any, demerol might have in the hyperactive or spastic human intestine has not been determined with nicety but preliminary studies in three instances indicate that relaxation may ensue (figure 8). Although demerol is not spasmolytic in the pyloric sphincter of dogs,[7] Barlow [9] states that "in 27 human subjects direct intubation studies with balloons in various portions of the gastro-intestinal tract reveal an antispasmodic response with 50 to 100 mg. of

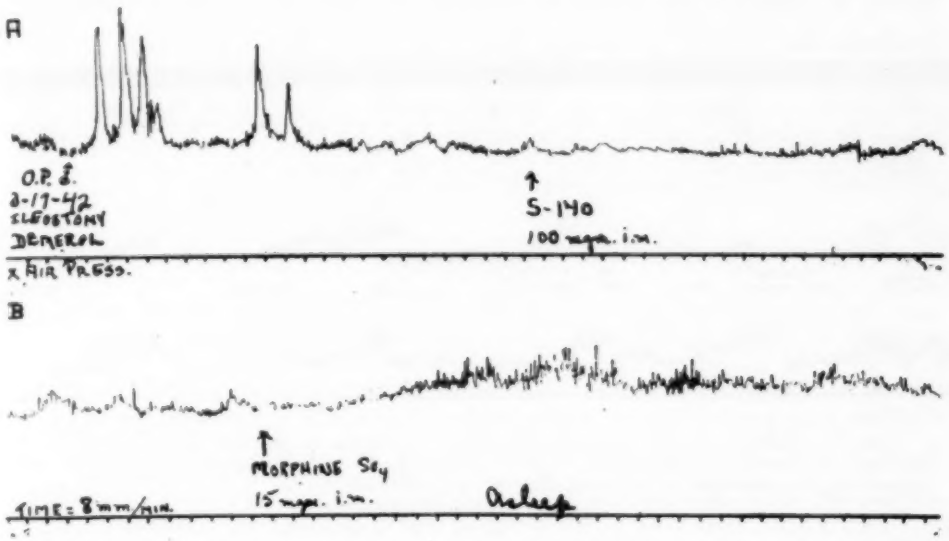

FIG. 7. Patient, O. P., age 32, ileostomy. Tracing of normal activity of ileum as relaxed by demerol (S-140), 100 mg. intramuscularly and subsequently stimulated by morphine sulphate, 15 mg. intramuscularly.

Time = 1 minute intervals.

demerol HCl intramuscularly in 23 or 84 per cent of the subjects. Complete cessation or diminution of motility occurred usually within 10 minutes and lasted from 15 to over 90 minutes." Barlow's findings have been amply confirmed by intubation studies in man by Batterman.[17, 18] A direct spasmolytic effect of demerol, in addition to its analgetic effect, would obviously enhance the relief obtained by altering the functional pathology responsible for the pain and discomfort. Even if relaxation did not uniformly occur, its analgetic effect might still be of sufficient degree to afford pain relief. In fact, in one experiment (figure 3) on an unanesthetized dog the analgetic effect of demerol was sufficient to allow for greater distention of the intestine before pain or discomfort was evinced. This prevailed even though demerol had increased intestinal tone.

In this experiment the dog's intestine had been quieted with atropine. The balloon was then deflated and reinflated with air from a large syringe until the dog gave visual evidence of slight discomfort. The average pain threshold of three inflations induced at three minute intervals was determined before and after demerol. The average volume of air causing discomfort in this particular experiment (figure 3) was 57 prior to demerol whereas 40 minutes after the drug the average figure was 78 c.c., even in the presence of increased tone produced by the analgetic agent. This difference of 21 c.c. of air represented a 36 per cent analgetic advantage gained by demerol. Although relatively crude in its present stage of development, refinements of this pressure balloon method may well give one a better appraisal of analgetic effects than the commonly used Hardy-Wolff light-beam technic [14] which evaluates analgetics not on their capacity to dampen visceral pain but only a specially induced pain (heat) on specially prepared skin areas. Since smooth muscle spasm and distention are common indications for analgetic therapy, one would be inclined to

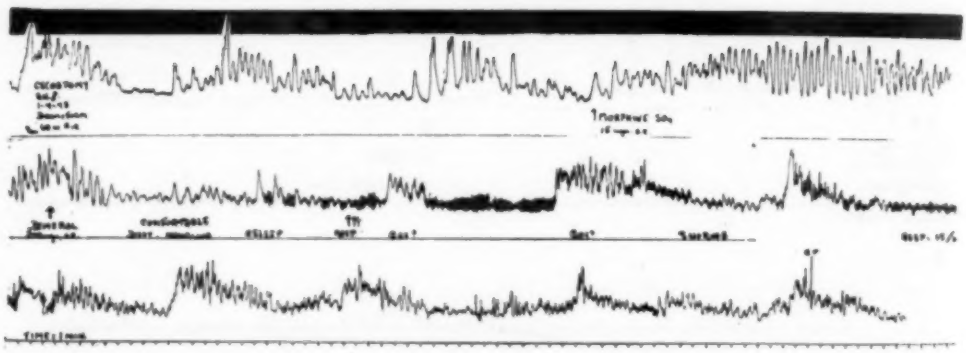

FIG. 8. Patient, A. N., age 42, cecostomy. Tracing of normal colonic activity as affected by stimulating action of morphine sulphate, 15 mg. subcutaneously and of subsequent partial inhibition by demerol, 200 mg. subcutaneously.
Time = 1 minute intervals.

believe that analgetic potency might best be evaluated from results obtained in artificially produced visceral pain as was done in these experiments. The results gained from several experiments of this type indicate a 20 to 36 analgetic potency for demerol.

The results of these studies warrant the clinical use of demerol, as is the case with morphine, in intestinal,[12] biliary,[15] and ureteral [16] colic, regardless of the action of the drug on smooth muscle.

COMMENT AND SUMMARY

Demerol hydrochloride is a safe drug. This is evident when one appreciates the high dosages administered to animals and man in toxicity studies and clinical assay.

Demerol is readily absorbed after oral, subcutaneous or intramuscular administration, producing analgesia and sedation. It exerts a weak atropine-like action as well as a moderately strong papaverine-like effect upon any

viscus containing smooth muscle. These actions are more intense when spasm or some form of stimulation prevails. However, should the functional pathology of a spastic viscus not be arrested, the failure of spasmolytic action may still be nullified or overridden by the marked analgetic action elicited by demerol.

The intestinal stimulating action of the drug uniformly produced in dogs does not prevail in man. The lack of stimulation of the intestine under demerol, particularly as regards tone increase, precludes its use as a bowel splint postoperatively. However, in the great majority of patients requiring analgetic drugs, splinting of the bowel is not a consideration and the absence of this action is an advantage since the usual constipating effect of morphine would be avoided.

The chemical configuration of demerol tends to render understandable some of its important actions in relation to atropine and morphine, its chemical relatives. It is another illustration of the fundamental principle that chemical structure or relationship frequently forecasts pharmacologic events to come. It is the principle which makes pharmacology interesting, even fascinating, and therapy rational.

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DEMEROL: A NEW SYNTHETIC ANALGETIC, SPASMOLYTIC, AND SEDATIVE AGENT. II. CLINICAL OBSERVATIONS *

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THE chemical composition and pharmacologic properties of demerol have been described in a separate communication.[1] The present report deals with clinical observations of the actions of this drug. Since 1939 a great number of clinical reports on demerol (variously called Dolantin, Dolantol, Alba, D–140, S–140) have appeared in the South American and European literature including observations on more than 2,000 cases. Only a few clinical studies, however, have been published in this country,[2, 3, 4, 5, 6, 7] including a series of papers by Himmelsbach and Andrews on tolerance and addiction liabilities in former morphine addicts.[8, 9, 10] We have attempted to compare our own results with those reported in the literature.

Material and Method of Study. A series of 146 patients was observed. One hundred eighteen of these were suffering from various diseases in which pain was severe enough to have justified the use of one of the opiates. This includes a group of 26 patients with persistent severe pain of weeks' or months' duration. Six of these patients had been taking morphine, 13 codeine, and two dilaudid for considerable periods of time. This group of 26 patients was given demerol at regular intervals for as long as 211 consecutive days. The average duration of therapy was 51.4 days, and the average total dose 32.6 grams. Most of the remainder of the 118 patients suffered from more acute illnesses and received an average total dose of one gram during an average period of six days. Twenty-four patients without pain were studied solely for the purpose of evaluating the sedative action of demerol. A final group consisted of four patients suffering from bronchial asthma. The special clinical records included a description of the type and severity of the pain, its duration, the effect of previous medications, a description of the subjective and objective response to the individual doses of demerol, and a summary of the analgetic, sedative, and side-effects noted. Routine laboratory and roentgenographic studies were performed and in over one-half of the cases the urinalysis, hemoglobin, erythrocyte, and leukocyte estimations were repeated during or after therapy with demerol. Evidences of toxicity were looked for, particularly in the group of 26 patients

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who received the drug for a longer time. In these cases complete urinalysis and studies of the blood, including determinations of hemoglobin, the number of erythrocytes and leukocytes, and differential leukocyte counts, were repeated at weekly intervals. Electrocardiograms and bromsulphalein tests of hepatic function also were performed repeatedly in these cases.

Dosage

Summary of the Literature. Demerol has been administered orally, intramuscularly or subcutaneously by most observers. The usual dose for adults was 100 milligrams; the dosage ranged between 50 and 200 milligrams. According to one report [11] heavy individuals usually required more than the average dose. Sprockhoff [12] states that doses for children range from 10 to 75 milligrams. Rectal suppositories have been used occasionally, especially in obstetrical cases.[13] When it is given intravenously, a number of unpleasant side reactions may occur and it is stated that when this route is employed the drug should be diluted and given slowly during a period of not less than two minutes.[14]

Present Study. In our cases the dose of demerol employed was, with very few exceptions, 100 milligrams, given orally or intramuscularly from one to eight times daily. In the chronic cases in which demerol was substituted for morphine or dilaudid, it was often necessary to shorten the usual four-hourly interval between doses to three hours. Because of a more prompt and, therefore, more easily evaluated response, the intramuscular route was used about twice as frequently as the oral route. Intravenous administration was avoided because of the possibility of its producing undesirable reactions and because the intramuscular injections usually produced their effects very promptly. Demerol may produce irritation when given subcutaneously and as a consequence this route also was avoided.

Analgetic Effects

Summary of the Literature. Favorable effects following the administration of demerol have been reported in a great variety of painful conditions, particularly those associated with spasm of smooth muscle. It has been reported that severe pain is satisfactorily controlled in various lesions of the gastrointestinal, biliary, and genitourinary tracts, as well as of the pancreas, pleura, and other organs.[3, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23] It has been considered to be effective in relieving pain associated with thrombosis or embolism of peripheral or coronary arteries.[15, 16, 21] It was used successfully in acute and chronic arthritides [16, 22] and in a variety of neurological disorders such as polyneuritis and neuralgia,[16, 19, 22, 24, 25] migraine,[16, 24] tabetic crisis and radiculitis.[24, 25] Its use for relief of pain occurring coincidentally in patients with multiple sclerosis led to the observation that it seemed to benefit the weakness and other symptoms of this disease.[24] It has been used extensively to combat pre- and postoperative pain and in other primarily surgical con-

ditions usually requiring morphine or its derivatives.[4, 5, 26, 27, 28] In obstetrics it has been used alone or in conjunction with scopolamine and barbiturates to control pain during labor and to aid in producing amnesia.[6, 7, 13, 31] It has been of value in gynecological conditions and procedures [11, 17, 29, 30] and in a variety of diseases of children.[12] Severe hiccups,[32] discomfort, and pain occurring during or after certain diagnostic procedures such as cystoscopy, retrograde pyelography, gastroscopy, bronchoscopy and pneumoencephalography have been claimed to be adequately controlled by demerol.[18, 22, 33]

Present Study

Table 1 summarizes the analgetic effect of demerol upon 118 patients with various diseases giving rise to the types of pain listed. Five patients

Table I

Analgetic Effect of Demerol

Types of Pain	Results			
	No. of Cases	Complete Relief	Partial Relief	No Relief
Arthritic	9	6	2	1
Gastrointestinal	22	15	6	1
Biliary tract	5	3	1	1
Renal	6	6		
Nerve and thalamic pain	18	11	6	1
Osseous pain	8	3	2	3
Headache	18	13	2	3
Pleural	12	8	2	2
Cardiac	10	5	4	1
Miscellaneous	15	9	4	2
Total	123*	79 (64.2%)	29 (23.6%)	15 (12.2%)

* Five patients had 2 types of pain.

had two distinct types of pain and consequently the number of instances exceeds the number of cases by five. Complete relief occurred in 79, or 64.2 per cent. Partial relief, which occurred in 29, or 23.6 per cent, usually consisted of moderate relief, sufficient to be considered as a satisfactory clinical response. No relief was obtained by 15, or 12.2 per cent. The groups with partial or no relief included four patients who had been addicted to morphine or dilaudid, and who resisted the attempted substitution of demerol for these drugs. Whenever codeine had been administered, demerol could be substituted without any trouble and was always claimed to be superior in its analgetic effect. The time of the onset of relief was from five to 20 minutes following intramuscular injection, and from 20 to 30 minutes following oral administration. The duration of the relief varied between one and six hours, but was usually three or four hours. Relief was more often complete, as well as more rapid, following intramuscular use.

The results in each type of pain are considered separately in the following paragraphs.

Arthritic Pain. Five of the nine patients in this group were suffering from acute gonorrheal arthritis and one each from streptococcal arthritis, tuberculous arthritis, traumatic arthritis, and polyarthritis associated with Hodgkin's disease. Relief of pain by 100 milligrams of demerol was complete in six, partial in two, and absent in one. The intramuscular route gave results which were superior to those obtained by oral administration in three of five patients in whom the comparison was made, and equal results in the two remaining patients. In five patients the analgetic effect of demerol was greater than a combination of one grain of codeine sulphate and 10 grains of acetylsalicylic acid.

Pain of Gastrointestinal Origin. Of the 22 patients in this group nine suffered from benign duodenal or gastric ulcers, 10 from carcinoma of the gastrointestinal tract, and one each from irritable bowel, uremic enterocolitis, and intestinal colic following abdominal paracentesis. In regard to the evidence for a spasmolytic action in this group, it should be stated that although an element of gastrointestinal spasm was undoubtedly present in a number of the others, the last three patients were the only ones in whom typical colic was present. Relief was complete in two of the patients. The third patient was a young woman with extremely severe cramps which were at first suspected of being due to lead poisoning, but later diagnosed as irritable bowel. She obtained no relief from 100 milligrams, and very slight relief from 200 milligrams of demerol given intramuscularly. The results in patients with peptic ulcer were uniformly good even when the ulcer was penetrating in type and accompanied by severe pain with radiation to the back or up over the anterior thoracic wall. The promptness of the effect after intramuscular injection and the failure of other measures to control the pain made it perfectly clear that demerol, rather than diet or antacids, was responsible for the symptomatic relief obtained. Variable results occurred among the patients with carcinoma of the gastrointestinal tract.

Biliary Tract Pain. Two of the five patients in this group had severe biliary colic. One obtained complete relief from demerol; the second, who was found at operation to have a complicating acute pancreatitis, obtained enough relief to be fairly comfortable although the physical findings over the abdomen were not obscured. One-fourth of a grain of morphine sulphate, given subsequently, produced complete relief, but also masked the abdominal findings. The difference in this case between the effects of morphine and demerol upon the physical findings is of some interest from the point of view of the diagnosis of acute abdominal conditions following the use of analgetic agents. Two other patients with less severe pain associated with acute cholecystitis were completely relieved by demerol. The fifth patient, who suffered from a dull steady pain due to primary carcinoma of the liver, was not relieved by oral medication with demerol.

Renal Pain. None of the patients in this group had typical severe renal colic. Four suffered from acute pyelonephritis, one from renal infarction and one from renal disease of indeterminate etiology. All obtained complete relief.

Nerve Root or Thalamic Pain. There were 18 patients in this group. Three suffered from severe pain of thalamic origin and each was completely relieved. Three had tabes dorsalis, and of these two were completely and one partially relieved. Four had sciatic pain and all were completely relieved. One patient with Buerger's disease and ischemic neuritis was not relieved. The remaining seven patients suffered from nerve root pain of various origin, including protruded intervertebral disc, transverse myelitis, and carcinoma with metastases to the spine or other structures adjacent to nerves. In spite of the severity of this type of pain, in the whole group 11 patients were completely relieved, six partially relieved, and only one not relieved.

A case illustrating the beneficial effect of demerol in pain of thalamic origin is that of a white male 62 years of age who suffered from hepatic cirrhosis and Parkinson's disease of arteriosclerotic origin. Very severe lancinating pains of thalamic type were present over the entire left side of his body. He had been maintained on three or four one-fourth grain doses of morphine sulphate daily. This amount controlled the pain, but the patient was depressed, "groggy," and disoriented. One hundred milligrams of demerol given orally every four hours did not give satisfactory relief, but the same amount given intramuscularly every six hours produced satisfactory relief of pain. In addition, his mental state changed to one of mild euphoria with considerable mental clearing. The sedative effect was not marked and additional medication was required for sleep.

Two other patients with so-called "intractable pain" of thalamic origin were very well controlled by oral administration of demerol for 211 and 175 days respectively.

Pain of Osseous Origin. In the eight cases in this group the diagnoses included several cases of metastatic carcinoma of bone, sarcoma of bone, and erosion of the spine due to aortic aneurysm. They were the group which was most resistant to demerol as well as to other analgetic drugs. Three were unrelieved, two partially relieved, and only three were completely relieved. In several instances it was found that morphine gave more relief than demerol.

Headache. Of the 18 patients in this group seven had headaches associated with arterial hypertension and of these, four had severe hypertension with marked retinopathy and other evidences of hypertensive encephalopathy. Other diagnoses included cavernous sinus thrombosis, meningococcic meningitis, subarachnoid hemorrhage, headache following spinal puncture, and others. In even the most severe headaches complete relief was almost always obtained. One patient with hypertensive encephalopathy required 0.2 gram for complete relief whereas the others with this condition were completely

relieved by the usual dose. Patients with less severe and less well-defined headaches were, as a rule, the ones incompletely relieved or unrelieved.

Pleural Pain. Eight of the 12 patients in this group suffered from pneumococcic pneumonia complicated by acute pleurisy. With one exception, complete relief from pain occurred within 10 to 15 minutes following the intramuscular injection of demerol, and sleep was induced in four patients. Respirations were slower, but not abnormally depressed. The failures occurred in patients with pleuritic pain due to pulmonary infarction associated with congestive cardiac failure.

Cardiac Pain. Five patients suffered from pain due to insufficiency of the coronary circulation. One such patient experienced prolonged anginal pain a few days following an acute myocardial infarction and was relieved after receiving demerol orally. Four patients suffered from repeated attacks of angina pectoris. An oral maintenance dose seemed to diminish the frequency and severity of these attacks. One of these patients was a 61 year old innkeeper with hypertensive and arteriosclerotic heart disease. During two control periods, totaling 41 days in which he received 10 grains of acetylsalicylic acid four times daily, he experienced 28 attacks of angina pectoris, whereas during two alternate periods totaling 59 days in which he received 100 milligrams of demerol four times daily, he had only 15 attacks. The patient was not aware of the nature of the drugs he received. The results in these cases of angina pectoris were suggestive, but not conclusive, of a beneficial effect of the drug. This may have been brought about either by its sedative or by its analgetic action or both. One patient was repeatedly relieved of severe pain due to acute pericarditis. Three of the remaining four patients suffered from chronic rheumatic heart disease with precordial aching pain and the last patient was diagnosed as having a cardiac neurosis.

Miscellaneous. Eight of the 15 patients in this group suffered from carcinoma of the bladder, or the female genital tract. Two suffered from dysmenorrhea, two from extensive dermatitis, and one each from burns, post-hemorrhoidectomy pain, and muscular pains associated with. sickle-cell anemia. The results in the patients with carcinoma were variable but generally good. One patient with dysmenorrhea was completely relieved, but the other was unrelieved. Both the pain and intense pruritus present in the cases with dermatitis were completely relieved. The patient with extensive second and third degree burns was only slightly relieved.

An example of the substitution of demerol for morphine in the treatment of patients with far-advanced malignant neoplasms is the case of a 54 year old white woman who was suffering from epidermoid carcinoma of the vagina. This tumor was given a microscopical grading of 4 (on the basis of 1–4), and it had metastasized and extended until it involved practically the entire pelvis, including the rectum and bladder. She complained of constant excruciating pain in this region. One and one-half grains of codeine sulphate produced very little relief, but one-sixth of a grain of morphine sulphate given every four hours caused satisfactory relief of pain. This

dosage was continued for 107 days, following which 50 milligrams of demerol were administered every three hours for five doses in place of the morphine, which had been given during the day and two doses of morphine were continued during the night. For about seven days the patient suffered from nervousness, anorexia, nausea, vomiting, diarrhea and severe mental depression. These symptoms were thought to be caused in part by the withdrawal of morphine and were treated with frequent small doses of phenobarbital. On the eleventh day of this régime she began to feel better and soon became entirely comfortable. At no time during the transition from morphine to demerol had pain reappeared. Phenobarbital was discontinued on the sixteenth day and on the twenty-second day the nightly doses of morphine were replaced by demerol without any further withdrawal

TABLE II

Analgetic Effect of Demerol

(127 Instances in 81 Patients)

Degree of Pain	Results					
	Complete Relief		Partial Relief		No Relief	
	No. Instances	Group %	No. Instances	Group %	No. Instances	Group %
Group 1 Very severe (44 instances)	26	59.1%	8	18.2%	10	22.7%
Group 2 Severe (50 instances)	29	58.0%	14	28.0%	7	14.0%
Group 3 Moderately severe (33 instances)	25	75.7%	6	18.2%	2	6.1%
Combined groups (127 instances)	80	63.0%	28	22.0%	19	15.0%

symptoms. The patient remained slightly euphoric, free of pain and relatively comfortable in spite of her steady downward course. A slight sedative action was present, but additional medication was required for sleep. She died on the seventy-sixth day of demerol administration and had been well-relieved of her pain until about six days before death when it became suddenly uncontrollable by any medication. Autopsy revealed nothing suggestive of toxic effects of the drug on any of the organs.

Analgetic Effect of Demerol in Various Grades of Pain. Table 2 shows the results obtained in 127 separate instances of varying grades of pain experienced by 81 of the patients. In contrast to table 1 in which relief was graded from a consideration of the over-all response of the patients concerned, table 2 is composed of the results following individual doses in which the degree of pain just before the drug was administered was recorded and

the effects of the particular dose noted. Although the grading of pain is necessarily only approximate, its validity seems to be borne out by the fact that the percentage of failures was higher in the groups with what was considered to be more severe pain. The total percentages of complete, partial, and no relief are very close to those obtained by the method of analysis used in table 1. It is significant that even in the severest degrees of pain complete relief was obtained in nearly 60 per cent of instances.

Sedative Effects

Summary of the Literature. The sedative effect of demerol in producing "pleasant drowsiness" or outright sleep frequently has been noted to amplify its analgetic action.[11, 13, 14, 18, 19, 21, 26, 27] The former effect, it seems, is due to a general reduction of all functions of the central nervous system, including the vomiting center. Because of the latter action demerol has been

Table III

Sedative Effect of Demerol in Presence of Pain

(99 instances in 81 patients)

Degree of Pain	Results					
	Sleep Induced		Sedation without Sleep		No Effect	
	No. Instances	Group %	No. Instances	Group %	No. Instances	Group %
Group 1 Very severe (33 instances)	18	54.5%	6	18.2%	9	27.3%
Group 2 Severe (37 instances)	15	40.5%	15	40.5%	7	19.0%
Group 3 Moderately severe (29 instances)	17	58.6%	9	31.0%	3	10.4%
Combined groups (99 instances)	50	50.5%	30	30.3%	19	19.2%

used to advantage in pneumoencephalography,[33] in whooping cough, and in habitual vomiting in children.[12] The sedative effect is not uniformly present and occasionally an increase in perceptiveness has been observed following therapeutic doses. This has resulted in anxiety and hyperexcitability [21, 28] or increased acuity in sensual perception similar to that observed with morphine.[9, 29]

Present Study. The sedative effects of demerol were studied in two groups of patients, one in which pain was present and the other, a smaller group of 24 patients, in which pain was absent. Table 3 shows the sedative

action in 99 instances of varying degrees of pain experienced by 81 patients. These instances were selected because the presence or absence of an effect was more clearly related to the administration of the drug than it was in others. This selection probably tends to exaggerate somewhat the favorable responses since questionable results are discarded. However, a certain degree of accuracy is indicated by the higher percentages of failures in the groups with more severe pain. Sleep was induced in from approximately 40 to 60 per cent, sedation without sleep in from about 20 to 40 per cent, and no sedative effect in from about 10 to 30 per cent of instances. The sedative effects in these patients were probably due in part to the relief from pain combined with a state of physical exhaustion incident to the illness rather than to a purely sedative action.

Twelve of the 24 patients whose illnesses were not accompanied by pain were suffering from cardiac disease with congestive failure. Among these patients sleep was induced in five, a variable effect occurred in three, no sedative effect was present in three and in one the results were indeterminate. Several patients in marked cardiac failure responded satisfactorily; however, relief was not as consistently present as when morphine sulphate was given, and this drug induced sleep in several patients not helped by demerol. Demerol seemed quite useful in two patients who were restless and disoriented during the terminal phase of uremia. They were not as deeply sedated as with morphine or barbiturates, but were quiet and slightly euphoric. Two patients with toxic delirium went to sleep promptly after intramuscular injection, and two other patients who experienced episodes of acute apprehension were similarly affected. In the entire group sleep was induced in 11, a sedative effect without sleep in four, no effect in three, a variable effect in three, and an indeterminate effect in three patients.

Bronchial Asthma

Four patients with bronchial asthma were given demerol. One patient who failed to respond to epinephrine or rectal ether anesthesia obtained definite relief following demerol with induction of sleep within about 20 minutes. A second patient had obtained no relief from epinephrine given as a spray and subcutaneously or from aminophylline given intravenously. The dyspnea persisted during the first four days of hospitalization during which demerol gave satisfactory relief lasting for varying periods. The third patient had also obtained no relief from epinephrine or aminophylline. The first dose of demerol gave no relief but two days later the next and several subsequent doses were effective. It is probable that both sedative and antispasmodic actions were operative in these cases. The fourth patient had only moderately severe asthma and was admitted to the hospital chiefly because of acute cystitis with marked dysuria. Demerol gave no relief from either symptom on two occasions.

Side-Effects

Summary of the Literature. Demerol in therapeutic dosage may produce a number of reactions not sedative or analgetic in character. These, it is claimed, were rarely marked and seldom interfered seriously with its use. The most common side-reactions mentioned are dizziness and sweating,[14, 20, 21, 26, 27, 28, 29, 34] nausea with or without vomiting, and vomiting without nausea.[14, 16, 19, 21, 27] Euphoria,[14, 15, 33] headache, anxiety and oppression are occasionally observed.[28, 29, 34] Intravenous injection has been claimed to cause a slight drop in systolic and diastolic blood pressure.[11, 30] Increase of respiratory and basal metabolic rates, lowering of glucose tolerance and decrease of gastric secretion in man have been noted.[20]

Table IV

Side-Effects of Demerol

(Experienced by 40 of 146 Patients)

Symptoms	No. of Instances	
Subjective vertigo	10	(1)*
Induration of tissues at site of injection	10	
Dryness of mouth	10	
Euphoria	8	
Nausea + vomiting	5	(3)
Paresthesias	4	
Nausea	3	
Sweating	2	
Muscular relaxation	2	
Palpitation and increased dyspnea	1	(1)
Vascular collapse with bronchial spasm	1	(1)
Insomnia and restlessness	1	(1)
Transient dimness of vision, pain at site of injection, drug eruption (?), delusions, urticaria—each	1	
	67	(7)

* Numbers in parentheses indicate cases in which side-effects necessitated stopping demerol.

Present Study. Table 4 summarizes the side-effects experienced by 40 individuals, who constitute 27.4 per cent of the total number of patients in our series. Since some patients noticed two or more of these symptoms the number of instances exceeds the number of patients. In only seven patients, or 4.8 per cent of the series were these effects sufficiently severe to require stopping the drug. With one exception the vertigo was mild and frequently preceded sleep by only a few minutes. Induration at the site of injection was noticed chiefly in patients who had received the drug several times daily for more than one month. It consisted of a firm, leathery, non-tender induration of the skin, subcutaneous tissues, and possibly underlying muscle. Also small subcutaneous hemorrhages which gave the area a bruised appearance were present in most of these cases. These changes were discovered late in the course of the study and thereafter, when carefully looked for, were seen in nine of 11 patients. Similar changes have not been

reported previously and it is possible that they resulted from the inadvertent injection of the drug into the subcutaneous tissues.

The euphoria was mild, perhaps better described as an "attitude of nonchalance." Nausea and vomiting occurred in five patients and was severe enough to require stopping the drug in three. Three other patients had nausea only. Palpitation and increased dyspnea followed each of two intramuscular injections given to a patient suffering from chronic rheumatic heart disease with congestive failure. A similar reaction was not seen in a number of other patients with heart disease. Another patient had received 100 milligrams of demerol intramuscularly from three to four times daily without any side-effects and with good relief of his lancinating tabetic pain. On the twenty-fifth day demerol was discontinued and replaced by one-grain doses of codeine. This was continued for 34 days when demerol was readministered intramuscularly in doses of 100 milligrams. The first dose was well tolerated. The second was followed by severe vasomotor collapse, bronchial spasm, nausea and vomiting. Subsequently these symptoms were reproduced on two occasions. Twenty-five milligrams of demerol caused no untoward symptoms but did not give the desired relief of pain. The occurrence of these reactions upon readministration of demerol suggests the possibility of some type of hypersensitivity in this patient. One patient was made increasingly restless and wakeful. In general, it should be emphasized that the incidence of serious side-effects was low.

Toxic Effects

Summary of the Literature. When demerol is given in doses of 100 milligrams or more from 10 to 20 times daily, certain reactions occur which must be interpreted as due to direct toxic effects of the drug. Many of the reported cases showed signs comparable to atropine or hyoscine poisoning, characterized by maximal dilatation of the ocular pupils, severe excitation, hallucination, disorientation as to time and place, muscular twitches and jerks, dryness of the mouth, tachycardia, disturbances in smell and taste and cold sensations.[34, 36, 37] In a carefully controlled study of drug addicts who received demerol in doses ranging from 825 to 2985 milligrams daily for from 10 to 11 weeks, Himmelsbach [8] demonstrated slight rises in blood pressure, pulse rate and temperature. Muscular tremors and twitches appeared in the second week. Reflexes became hyperactive and stimuli ordinarily not disturbing were found to cause an excessive response. One patient developed a "mild toxic psychosis" and two were claimed to have petit mal seizures during the tenth week. One patient reported by Kucher [37] experienced a frank epileptiform seizure following overdosage of demerol; however, this patient also had been taking "Phanodorm" for a considerable period of time. Using the same group of patients as Himmelsbach, Andrews [10] reported the results of electroencephalographic examinations. These revealed abnormal records with an increase in the percentage of low frequency

(delta) waves. In general, the electroencephalographic changes were much more marked than those occurring after large doses of morphine and indicated "a profound effect on the central nervous system when used in quantities sufficient to satisfy the desires of addicts." This pattern differed significantly from that observed in addicts under the influence of codeine or morphine whose records showed an increase in voltage with decrease in the frequency of the basic (alpha) rhythm.[38] No significant changes have ever been observed in routine laboratory tests or in serial electrocardiograms.

Present Study. None of our patients received doses comparable with those cited above. This may account for the absence of "toxic" reactions of the types described. The laboratory findings in both the larger group of patients and the group of 26 patients for whom these tests were repeated at regular intervals did not show any changes which could be interpreted as being due to demerol.

Addiction

In 1938 the Committee on Drug Addiction of the National Research Council stated that it had not been possible " . . . to prepare a drug with the power to control pain requisite for a morphine substitute without at the same time introducing factors which cause the appearance of other phenomena leading to addiction." [39] This statement referred to all substances derived from opium directly or obtained by altering the structure of the morphine molecule. Most analgetics of this type at one time or another have been claimed not to be habit forming. This was true of heroin,[40] dilaudid,[41] and codeine.[38]

Structural similarities between morphine and demerol have been considered previously.[1] Demerol also has been claimed not to be habit forming,[14, 17, 18,22, 26, 27] but a few cases suggestive of addiction have been reported.[19, 35, 36, 37, 42, 43] In all of these cases withdrawal symptoms were present following periods of excessive dosage and all cases observed were either those of severely psychopathic patients or former morphine addicts. "Typical withdrawal symptoms" occurred, but they were milder and easier to overcome than those with morphine. Recently Himmelsbach (in the study mentioned above under "toxic effects") reported on the addiction liability of demerol.[8] Again, these subjects were former morphine addicts. All developed the triad of tolerance, habituation and dependence requisite for the diagnosis of addiction.[39] The doses were excessive and symptoms of withdrawal were mild. The same subjects were studied by Andrews [9] for the development of tolerance. He stated that "The tolerance developed to demerol is maintained beyond the period of administration but appears to be less permanent than that developed to morphine." It must be stressed that so-called "primary addiction" following ordinary therapeutic dosages has not been reported. Thus Batterman [3] found no instances of primary addiction among his patients receiving the drug in controlled doses for several weeks

or months, but noted a few cases in which a desire for the drug was expressed. He stated that habituation, as distinguished from addiction, may be produced by demerol and that the possibility of the occurrence of addiction after extended administration in patients with chronic illness had not been excluded. Demerol has been placed under the narcotic law in Germany.[44]

The group of 26 patients who received demerol for the relief of pain over a considerable period of time was not well suited for a study on tolerance, habituation and dependence.

Tolerance, a gradual decrease in the effectiveness of a given dose produced by repeated administration of a drug, may have been present in nine of the patients of this group for whom the dosage of the drug had to be increased from time to time, but in only one was it certain that the need for larger amounts was not due to an increase in the intensity of the pain.

Habituation, or "mental conditioning to the repetition of an effect," [39] could not be tested since the patients required an analgetic at all times and were in acute discomfort when they did not receive it. On occasions when an injection of saline was substituted the patients invariably complained of severe pain.

Dependence is determined by the appearance of certain signs and symptoms upon withdrawal of a drug. It was thought that dependence could not be tested in our patients since opiates had to be substituted immediately upon withholding demerol and thus might have masked any symptoms of withdrawal.

TABLE V

Symptoms Following Withdrawal of Demerol in Nine Persons

	Periods of Demerol Administration (in Days)						
	1–10	11–20	21–30	31–40	41–50	51–60	Over 60
Drug addiction*	0 (s)	+++ (s)					
Ca. of tongue			+ (c)				
Peripheral neuritis			+ (c)				
Ca. of bladder		+ (c)		+++ (m)			
Ca. of breast		++ (c)	+++ (d)		++ (c)		
Ca. of cervix	0 (s)			++ (c) ++ (c)		++ (c)	
Subacute bacterial endocarditis					++++ (c)		
Transverse myelitis					+ (m)		+++ (m)
Ca. of tongue*							++ (m) 66th day ++++ (d) 100th day ++++ (m) 120th day ++++ (d) 170th day

* See text.

s saline injection
c codeine
d dilaudid
m morphine
} used as substitutes

0 no reaction
\+ opiates ineffective for several hours
++ nausea, vomiting, sweating
+++ nausea, vomiting, irritation, nervousness
++++ nausea, vomiting, irritation, nervousness, itching of skin

However, among 21 patients from whom demerol was withdrawn a total of 38 times there were nine who developed reactions of varying intensity (table 5). In eight of the patients demerol was replaced by one of the opiates and in one patient no medication was given. The reactions seen on withdrawal of demerol consisted of nausea, vomiting, perspiration, jerking and tremor of muscles, nervousness, irritation, depression and itching of the skin. The symptoms usually began several hours after the last injection of demerol and one or two hours after the first injection of opiates which were substituted without the patient's knowledge. They usually lasted for 12 to 24 hours, occasionally for 48 hours, and were readily controlled by the administration of barbiturates and hyoscine. There appeared to be a higher incidence of these symptoms in patients who had received demerol for a longer period of time. This is indicated by the fact that in the total group of 21 patients only six of the 19 withdrawals before the thirtieth day but 12 of 13 withdrawals after 30 days were followed by symptoms. In three patients who received demerol orally withdrawal at various intervals up to 211 days was not followed by any untoward reactions.

The only patient (first case in table 5) in whom opiates were not substituted after withdrawal of demerol was a 36 year old American nurse complaining of severe low back pain. This pain was found to be caused by a protruded intervertebral disc which had been present for several years and had led to morphine and codeine addiction. However, she had not been taking opiates in any form for several months prior to entering the hospital. When demerol was administered it afforded immediate and complete relief which lasted for three hours following each injection of 100 milligrams. Some nausea and vomiting were noted following the first injections. The first withdrawal of demerol on the second day (replaced by sterile saline injections) was followed by prompt return of pain. During the second week of administration the patient noticed restlessness, depression and a feeling af anticipation about one hour before the next injection was "due." This she described as "craving" and recognized it as being similar in type to the sensation she had experienced during morphine addiction. On the fourteenth day of treatment the drug was replaced by sterile saline injections. The last injection of demerol was given at seven o'clock in the morning and four hours later she began to perspire freely, noticed jerking of her muscles, and became quite apprehensive. One hour after this, the pain returned and the patient became extremely depressed and agitated and felt herself "abused." She cried vehemently, was nauseated, and vomited profusely. All these signs increased to an alarming degree until two o'clock in the afternoon when hyoscine and phenobarbital were administered. During the afternoon she gradually became calm and except for pain was relatively comfortable the next morning.

In this case the reaction could not possibly be attributed to opiates since none was administered. The appearance of these symptoms after only two

weeks of demerol administration is unusual and could perhaps be explained partially as a psychologic response to the return of pain.

A representative case, in which reactions of this type were observed while pain was adequately controlled, is that of a 61 year old American bar tender who suffered from carcinoma of the tongue with regional metastases. For months he had complained of intense pain in his mouth, neck and face which was not appreciably altered by several courses of roentgen and radium therapy. During a period of 27 days morphine sulphate in one-quarter grain doses every four hours gave good relief from the pain and produced no ill effects. Then morphine was withdrawn and demerol substituted. The only symptoms suggestive of morphine withdrawal which the patient experienced at this time were insomnia and slight restlessness. These symptoms persisted for only a few days and disappeared following the administration of phenobarbital. Relief of pain lasted for two or three hours, but was not as complete as with morphine. On the sixty-sixth day of treatment at two o'clock in the afternoon demerol was replaced by morphine in one-sixth grain doses. Later in the day the patient became nauseated and restless. The next morning severe vomiting occurred and was associated with pronounced hyperhidrosis and fine tremor of the extremities. This seemed to be aggravated by each morphine injection although these had been well tolerated before. Pain was controlled throughout and the patient began to feel well again on the afternoon of the second day. Three days later demerol was again substituted for morphine without the appearance of any untoward symptoms. On the one hundredth day demerol was withdrawn a second time. The last dose of demerol was given at six o'clock in the morning and one-twentieth grain of dilaudid which the patient had tolerated well at other times was substituted from nine o'clock on. At 11 o'clock the patient complained of severe nausea and vomited several times during the rest of the day. He spent a fair night but the next morning began to experience increased nervousness, perspiration, muscular tremors, and an intense itching of the skin. At noon he vomited several times and became extremely depressed and agitated. Demerol was administered and all symptoms subsided within one hour. A third withdrawal of demerol on the one hundred twentieth day with morphine as the substitute and a fourth on the one hundred seventieth day using dilaudid were followed by almost identical reactions. On the latter occasion administration of sodium amytal and hyoscine was necessary during the first day. All signs and symptoms abated on the second day following withdrawal of demerol.

The reactions observed were undoubtedly related to the withdrawal of demerol. They may have been influenced or intensified by opiates given during the withdrawal period. This is suggested by the usual appearance of the symptoms one or two hours after their administration. On the other hand five of these patients had received either morphine or codeine prior to demerol administration and had not shown any signs of intolerance. Hence it is difficult to evaluate the rôle the opiates may have played. Further, the

fact that these reactions were not prevented by either morphine or dilaudid, drugs which might be expected to satisfy dependence needs, complicates the interpretation of these symptoms as part of an abstinence syndrome. Also, the early appearance of nausea and vomiting and the absence of yawning, lacrimation, rhinorrhea, etc.,[8] are not characteristic of the picture seen following withdrawal of morphine. However, the circumstances under which these reactions occurred suggest the possibility that addiction to demerol may have been present. Further studies concerning the addicting properties of demerol in subjects who do not require additional medication for the relief of pain and who have no previous history of habituation or dependence on other drugs seem definitely to be indicated.

Summary and Conclusions

1. In 123 instances of severe pain occurring among 118 patients complete relief followed the administration of demerol in 79 (64.2 per cent), partial relief in 29 (23.6 per cent), and no relief in 15 (12.2 per cent). The customary dose was 100 milligrams given orally or intramuscularly.

2. The onset of relief was from five to 20 minutes following intramuscular injection, and from 20 to 30 minutes following oral administration. Its duration varied between one and six hours, but was usually three or four hours. Relief was more often complete following intramuscular injection.

3. The analgetic potency of demerol in the dose employed was greater than that of one grain or more of codeine, or combinations of codeine and aspirin. It was usually less than that of morphine in one-quarter or one-sixth grain doses.

4. The sedative action of demerol was studied in the group of 81 patients with pain and in 24 patients without pain. The group of patients with pain received, as a rule, only a few doses of demerol. Its administration was followed by sleep in about 50 per cent, by mild sedation in about 30 per cent, and by no noticeable sedative effect in about 20 per cent of instances. The hypnotic or sedative effects following repeated administration were not profound, a fact which was of advantage in the treatment of patients with chronic painful diseases.

5. Three patients suffering from status asthmaticus were benefited by demerol, although a fourth asthmatic patient was not.

6. Side effects were noted by 40 (27.4 per cent) of the 146 patients, but in only seven (4.8 per cent) was it necessary to stop the drug. Two patients developed reactions which were somewhat alarming.

7. Laboratory studies showed no changes which could be attributed to demerol, although the drug was given at regular intervals for as long as 211 consecutive days and 26 patients received an average total dose of 32.6 grams.

8. In nine of 21 patients who had received demerol for varying periods of time the withdrawal of the drug and the substitution of one of the opiates

were followed by certain undesirable symptoms, the significance of which is discussed.

9. It is concluded that demerol is an effective analgetic drug which is relatively non-toxic. It may possess addictive properties but these are apparently not as marked as those of some of the opiates, morphine and its derivatives. It may be said that demerol is capable of replacing these drugs in a great number of painful conditions.

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SERUM AMYLASE IN MUMPS*

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This study was inadvertently instituted when high levels of serum amylase were noted in several cases of epidemic parotitis, utilized as controls for mumps complicated by pancreatitis. In this latter group a marked increase of serum amylase was expected. A review of the American literature of the past two decades uncovered no specific study or detailed analysis. The literature was, of course, voluminous with articles dealing with the test, its variations and its relationship to disease. Acute pancreatitis was the outstanding condition in which a high level was clinically significant. However, the tests were performed in a great variety of pathological lesions. Lewison [1] contributed a clinical article of interest and discussed a variety of conditions. Elman,[2] Popper,[3] Comfort,[4] McCorkle,[5] and others demonstrated its value in pancreatitis. Special studies have been made in such diverse diseases as rabies,[6] thyroid activity,[7] diabetes,[8] shock,[9] diseases of the brain,[10] liver disturbances,[11] bacterial infection,[12] parturition,[13] tuberculosis,[14] chronic alcoholism,[15] etc.

Among the many publications there were several references to increased levels in mumps. A brief report was submitted by Lewison,[1] who devoted a short paragraph, unattended by statistics, in a general article on the clinical value of the serum amylase test. He observed 12 instances of epidemic mumps. Bodansky and Bodansky [16] quote the work of Brinck and Gülzow, who noted increased levels in every one of nine cases which they investigated. Branistéanu and Boutroux [17] reported elevated values in a general study. Specific references were found in foreign literature. Dunlop,[18] in 1933, and Hershhorn [19] et al., in 1931, contributed brief reports. It is not within the realm of this presentation to elaborate upon the general historical background. Reference can be made to such notable contributors as Bernard,[20] Foster,[21] Wohlgemuth,[22] Davison,[23] Elman,[24] Muhlfeld,[25] Somogyi [26] and many others.

The chief sources of this digestive enzyme are the pancreas and the salivary glands, particularly the parotid. A brief description of the histopathology and the secretions of the salivary glands furnishes a basis for better understanding. The secretions of the parotid and submaxillary glands can be obtained separately by inserting a canula in the openings of the ducts in the mouth or, according to the method of Pavlov, by transferring the end of the duct so that it opens upon the skin, thus creating a salivary fistula. Examination of the separate secretions shows that the main difference lies in the fact that the parotid saliva contains no mucin, whereas the submaxillary

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and especially the sublingual glands are rich in mucin. The parotid saliva of man is particularly rich in ptyalin (salivary amylase) as compared to the other glands. Thus, the parotid is described as a typical serous gland and is the chief source of the starch-splitting enzyme; the submaxillary is a mixed type; and in the sublingual glands mucous cells predominate.

The precise pathological changes of the parotid glands in mumps are still controversial, as opportunities for examination are rare. From existing evidence it would appear that the gland substance is the seat of intense hyperemia and edema, with serous and cellular infiltration of the interstitial and interglandular tissue, as well as edema of the bordering extraglandular soft tissue. A catarrhal inflammation of the ducts and their branches, which contain in their lumina desquamated epithelium and round cells, has also been observed.

Any mechanical obstruction producing retrograde passage into the lymph and blood streams, liberation of diastase * as a result of acute damage to the parenchymatous cells secreting the enzyme, or hypersecretion will all tend to induce increased content in the blood. These factors are at play during parotid involvement in epidemic mumps, and blockage assumes a very important rôle. As a matter of fact, appreciable increases in the diastase level were observed in cases of calculous obstruction [27] to the salivary duct. The objective findings of inflammation and edema causing stenosis of the external orifice and swelling of the parotid gland proper have been noted since the early description of the disease, and harmonize in principle with the physiopathological concept for the abnormally high serum amylase results.

Method

The procedure employed was the determination of blood diastase by the saccharogenic action method of Somogyi as described by Gradwohl [28] in his textbook. The only modification was the last step, where the Folin-Wu copper reduction process was substituted for the method employed by Somogyi in the determination of the reducing sugar. The results were expressed in terms of milligrams of glucose per 100 c.c of plasma. No claim is made for precise quantitative accuracy, as the possibility of sources of error is well recognized. The following quotation from Lewison [1] is completely sponsored: "Technical variation has inevitably been responsible for some dissension among observers; yet if serum amylase values are regarded only with comparative and not quantitative accuracy, this reliability assumes a new importance and may well satisfy a most helpful diagnostic rôle. A lack of ultimate quantitative precision should not impugn the clinical value of the serum amylase test." The test was performed at Gorgas Hospital by the same personnel in a constant manner, so that the comparative figures can be considered of definite value.

* Diastase and amylase are employed as interchangeable terms.

Control Group

This group was chosen at random from patients of various wards. Table 1 reveals an analysis of 65 consecutive cases:

Table I

Serum Amylase Levels in Control Series of 65 Cases

Diagnosis	No. of Cases	Average Serum Amylase (mg. per 100 c.c.)
1. Acute appendicitis	2	66
2. Acute cholecystitis	9	59
3. Diabetes mellitus	4	51
4. Fever of unknown origin	4	68
5. Acute gastritis	4	48
6. Gastroenteritis	3	53
7. Malaria	3	52
8. Miscellaneous conditions	18	55
9. Psychoneurosis	3	58
10. Acute pancreatitis	14	281
11. Intestinal obstruction; possible pancreatitis	1	303

There were 14 cases of pancreatitis and one possible pancreatitis exhibiting high levels. Excluding these, the average of the remaining 50 with a wide range of disease was calculated as 56.4 mg. The minimal figures were 15 and 16, noted respectively in carcinoma of the liver and cholecystitis with hepatic damage. The maximum was 117 in acute cholecystitis. Gradwohl [28] places the normal range between 80 and 150. As the average in this series was 56.4 and it was felt that no rigid mathematical restrictions should be imposed the range of 40–175 was adopted as the normal limits for this study.

Material

Sixty (60) consecutive patients who were admitted to the Isolation Section of Gorgas Hospital with a diagnosis of mumps served as the source of this study. There were 95 per cent (57) adults and 5 per cent (three) children. The average age was 24 years. There were 88 per cent (53) males and 12 per cent (seven) females. The negro race comprised 67 per cent of the entire group and the white race 33 per cent. Therefore, the representative individual dominant in this group was a negro, male, young adult.

Results

In table 2 the results of serum amylase findings in various subgroups of mumps are recorded. Of the 60 cases admitted as mumps, seven were ill from other causes and three had mild unilateral involvement which completely subsided at the time blood was drawn for chemical analysis. Of the 50 remaining cases, the average serum amylase, calculated during the active stage of the disease, was 502 mg., which is almost 10 times greater

TABLE II

Serum Amylase Levels in 60 Consecutive Cases Admitted with Diagnosis of Mumps

Diagnosis	No. of Cases	Average Serum Amylase (mg. per 100 c.c.)
1. Clinical Cases of Mumps with Elevated Levels		
a. Unilateral parotitis		
(1) Without extension	17	392
(2) Extension to submaxillary and/or sublingual	4	494
b. Bilateral parotitis		
(1) Without extension	7	811
(2) Extraparotid salivary extension	9	642
c. Extraparotid salivary disease		
(1) Submaxillary gland	2	68
(2) Sublingual glands	1	127
d. Parotitis complicated by orchitis, encephalitis, etc.		
(1) Unilateral	2	325
(2) Bilateral	6	684
2. Epidemic Parotitis with Normal Levels		
a. Unilateral—completely subsided	3	107
b. Bilateral—active phase	2	95
3. Cases Admitted as Mumps but Later Clinically Disproved		
a. Secondary lymphadenopathy, pre-auricular and cervical	4	83
b. Cellulitis of face secondary to infection of teeth	3	73

than the average of the control series. The average for bilateral involvement was 707 mg. compared to 421 mg. when a unilateral infection was present. When the disease of the salivary glands was exclusively extraparotid, as in two cases of submaxillary inflammation and one of sublingual, the results were normal. The results of the seven cases admitted as mumps

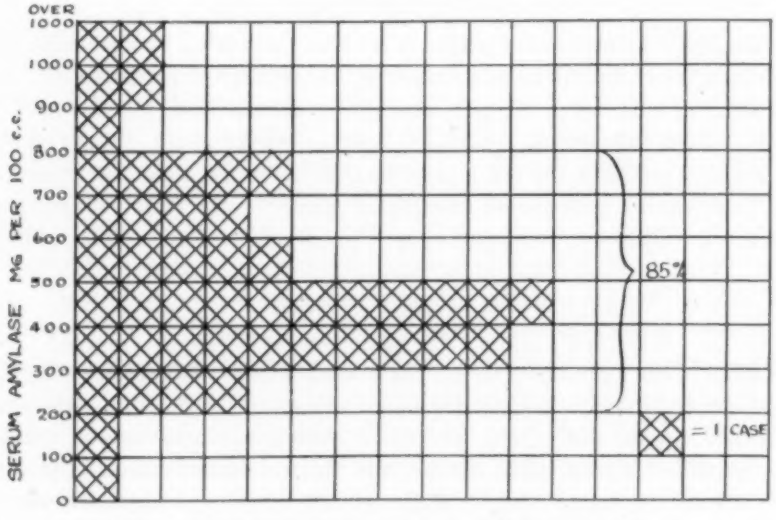

FIG. 1. Serum amylase levels in epidemic parotitis.

but proved by further observation and study to fall into another category were also normal, as were the three unilateral cases, which were discarded in the final analysis because of the tardiness of the studies. However, there were two bilateral cases, typical of mumps, presenting normal levels for which no explanation can be offered. They fell in an older age group that seemed to show lower trends. Therefore, of 47 cases of active parotid involvement, normal figures were demonstrated in only two. Markedly ele-

TABLE III

Relationship of Reaction of Orifice of Stenson's Duct to Serum Amylase Level

Reaction (Orifice)	No. of Cases	Average Amylase (mg. per 100 c.c.)
0 (negative)	6	269
± (mild)	12	416
+ (moderate)	22	584
++ (severe)	5	737

vated levels occurred in 95 per cent. The two highest, 1297 mg. and 1852 mg., were detected in bilateral cases. Extrasalivary complications of mumps did not seem to alter results, nor did extension to extraparotid salivary glands.

Figure 1 represents a compilation of diastase levels during the active phase of parotitis (47) cases.

An attempt was made to correlate the elevation of the serum diastase with the degree of edema and inflammation around the orifice of Stenson's duct.

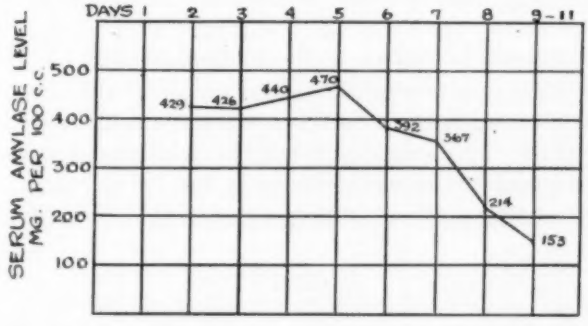

FIG. 2. Relationship of day of disease to serum amylase level in unilateral parotitis.

This reaction was expressed as 0 (none), ± (mild), + (moderate) and ++ (severe). Table 3 records these findings in 45 cases, for which accurate data were available.

The trend suggests the possibility that the more severe the reaction around the orifice, producing obstruction, the higher the level. However, the sample is small, in several cases there was a marked discrepancy, and it is possible for the duct proper to be blocked without apparent reaction at the orifice.

The relationship of the day of the disease from onset to the diastase level was studied in both unilateral and bilateral parotitis. Daily serial determinations were not made on each case and a cross section of the entire series was analyzed. In bilateral states, the day was recorded from the time both glands were involved. Some cases had several levels and others had only one, with chronological data usually based on history. Figure 2 (unilateral) and figure 3 (bilateral) reveal the average amylase level in relationship to the day of the disease.

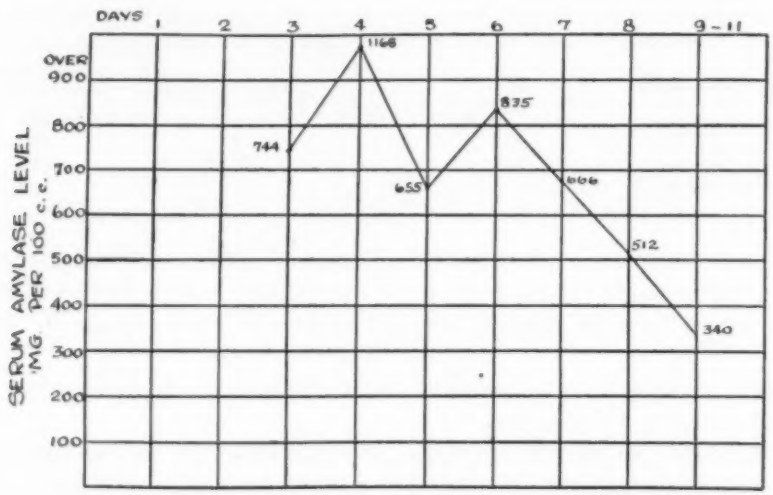

FIG. 3. Relationship of day of disease to serum amylase level in bilateral parotitis.

No conclusions can be drawn as the method is open to criticism and the sample is inadequate. However, the curves suggest that the serum amylase level is high early in the disease, that it is maintained for a week or more during the active phase, and subsides gradually with the disappearance of the swelling. In the cases of bilateral parotitis, the curve reaches a higher level and seems to be maintained over a longer period than in unilateral cases.

COMMENT

On the basis of these studies one cannot avoid the conclusion that an elevation of serum amylase is present in the great majority of cases of epidemic mumps. It is especially to be expected since the parotid gland which is the chief salivary enzyme producer is frequently affected. The finding is naturally of academic interest and has a sound basis. Although the diagnosis of mumps is usually simple, there are cases which present differential problems. In this series of 60, there were seven patients who presented clinically suspicious findings and had positive contact histories. The normal serum amylase helped to rule out contagion and the subsequent course and objective findings confirmed the reliability of this test. Elevated levels also

assisted in establishing a diagnosis of mumps in the early development of two doubtful cases. Thus, the test has both a positive and negative value. No explanation can be offered for the two normal levels which occurred in individuals past the third decade of life. Therefore, a normal level can be found in exceptional instances of epidemic parotitis, perhaps important in older age groups. It also seems reasonable to assume that normal levels are the rule rather than the exception in extra parotid salivary mumps and in cases which are admitted for extension and complications such as orchitis, meningo-encephalitis, etc., after the parotid disease has subsided. Particularly during epidemics the diastase level may assist in establishing or excluding the diagnosis of mumps in an observation case. Cellulitis of the face, infection of the teeth and gums, pre-auricular and cervical lymphadenopathy are among the conditions which may at times create confusion.

When one is reasonably sure that pancreatitis is not present, an elevated level always points to parotitis; and conversely in a patient with gastrointestinal symptoms the diagnosis of pancreatitis can be offered in the absence of parotid involvement. The clinical picture will usually allow differentiation without difficulty. The complication of pancreatitis in mumps is not a rarity. The clinical manifestations of the syndrome are highly suggestive, but an increase in serum amylase over a recent level taken during epidemic parotitis offers confirmatory evidence.

Primary extrasalivary mumps has been reported in the literature. Primary encephalitis,[29] pancreatitis,[30] meningitis,[31] orchitis [32] have been observed. Neurological complications as myelitis [33] and polyneuritis [34] also have been noted in print. Often the evidence for the etiology is not firm. Some of these cases may have a mild parotitis and an elevated level can then be confirmatory. Others may develop parotitis following the initial extrasalivary lesion and in these cases this adjuvant diagnostic procedure can be convincing. Thus, there are innumerable ramifications for the judicious employment and clinical correlation of the test.

Summary and Conclusion

1. A brief review of the literature on serum amylase in mumps and a basis for this elevated finding were submitted.

2. A study and an analysis of a control group of 65 cases and of a series of 60 patients admitted with the diagnosis of mumps were made.

3. Elevated amylase levels were found in the great majority (95 per cent) of cases of epidemic parotitis during the active phase. This observation is not only of academic interest but can definitely be helpful in a selected group, which has been discussed.

4. In exceptional instances results may be capricious and the clinical pattern must then be relied upon.

5. Awareness by the general medical profession of the value of the serum amylase test in mumps and its limitations is desirable.

Grateful acknowledgment is due to Colonel Dooling, M.C., Chief of the Medical Service, for his guidance and encouragement; to James E. Jacobs, B.S., Chemist; and to the personnel of the chemistry department, Gorgas Hospital, Ancon, Canal Zone, for their splendid coöperation.

Gratitude is also expressed to Estelle Hall, medical secretary, for her aid in the compilation and organization of data.

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RHEUMATIC FEVER: DIET AS A PREDISPOSING FACTOR *

By Don Carlos Peete, *Kansas City, Missouri*

Although many careful studies have been made of rheumatic heart disease throughout the world, many misconceptions of the etiologic factors of the disease still exist. If one studies the reports from India,[1, 2, 3] Australia,[4, 5, 6, 7] Costa Rica,[8] Mexico,[9] Argentina,[10] Hawaii,[11] Iceland,[12] Greenland,[13] England,[14, 15, 16, 17] and the vital statistics of the United States,[18] he is quickly convinced that climate is but a secondary factor. Focal infection has been a greatly overemphasized factor. Careful studies have shown that many patients had their first attack of rheumatic fever after the tonsils were removed and many patients continue to have recurrence after tonsillectomy.[33, 46] It is generally agreed that it is good practice to remove infected tonsils in order to improve the general resistance of the individual to respiratory disease. The recent emphasis placed upon heredity by Wilson,[19] Reed et al.,[20, 21] and Irvine-Jones,[22] does not explain the high incidence among the poor nor the gradual decrease in the death rate in the last 30-year period in the United States, England and Australia. Glover,[14] in 1930, suggests that this incidence is 30 times greater among the poor than among the well-to-do. The studies of others would seem to confirm this statement. Juster's [23] recent studies indicate that upper respiratory infections complicate preëxisting rheumatic infections rather than initiate them. If this is a fact, the rôle of the hemolytic streptococcus organism in the etiology of the disease is questioned. It may activate the rheumatic state in a manner similar to that in which respiratory infections activate tuberculosis.

Rinehart,[24] in 1934, suggested that vitamin C deficiency predisposed the individual to a hemolytic streptococcus that caused rheumatic fever. Although his work has not been duplicated or confirmed in clinical experience by other investigators, we were then of the belief that there was a dietary factor that played an important part. For several years patients with rheumatic disease have been studied from the point of view of deficiencies in vitamin D, calcium and phosphorus. For a period of four years now, patients seen in both clinic and private practice, showing any signs of rheumatic fever or rheumatic heart disease, have been instructed to take daily sun baths when possible and to include one quart of milk, one egg, and cod liver oil in the daily diet. These patients were, generally, above eight years of age. There was such a marked lowering of the incidence of recurrence of the disease that it was decided to make a survey of the dietary habits of similar patients before correcting their diets. It is our belief that one's dietary habits become more or less fixed early in life and that many of the con-

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ceptions and prejudices toward food are acquired and kept throughout life until old ideas are replaced by new ones. We have found, also, that many people really do not know of what their diet consists since their eating has become so automatic.

Chart 1 is the list that is given to our patients with the instructions to check, after each meal, the foods eaten and to write in any not listed. We met with better coöperation when the importance of this record was impressed upon the patient. When this method is used, the deficiency in the diet is immediately revealed. The patient is then asked to keep a record, after his diet has been corrected, until his habits have been definitely altered.

Chart 2 shows the result of such a survey of 50 patients, some in the acute and some in the chronic rheumatic state, as compared with 25 normal school children in a middle-class public school. This chart is a comparison of the number of times per month the average patient with rheumatic infection takes the food indicated as compared with the average school child's diet.

A study of this table shows that the average diet of the rheumatic patient is very low in those foods that supply vitamins A and D, and the minerals, especially calcium, phosphorus and iron. There is also some deficiency in proteins and an excess in starchy foods and in the refined sugars. Both diets show a restricted use of eggs (this may have been due to the extremely high cost of eggs at the time this survey was made).

It was found, also, that many families were eating butter substitutes which have a lower vitamin and mineral ratio than butter. The economic influence is seen in the consumption of bacon: being expensive, it was treated almost as a luxury by the normal group, while a greater amount was available to the low income rheumatic group through relief measures, since it is a meat that does not require the same amount of refrigeration as fresh meat.

These findings, in some respects, are very similar to the results of the studies of Warner, Winterton and Clark [31] in 1935. The striking similarity is especially noteworthy in view of the fact that the work of these men did not come to my attention until after I had completed my own series of studies.

DIRECTIONS FOR THE USE OF THE DIET SURVEY CHART

After each meal make a single straight mark like "/", in the column opposite the different foods eaten, on the correct day of the week. Use one mark to indicate one serving. If you ate foods which are not on the chart, write them into the blank lines provided on the edge of the chart.

Example:

	Monday	Tuesday
Bread	////	///
Beef	/	
Potatoes	//	//

This would indicate that on Monday you had four slices of bread, one serving of beef, and two servings of potatoes during the day. On Tuesday, you had only three slices of bread, no beef, and two servings of potatoes.

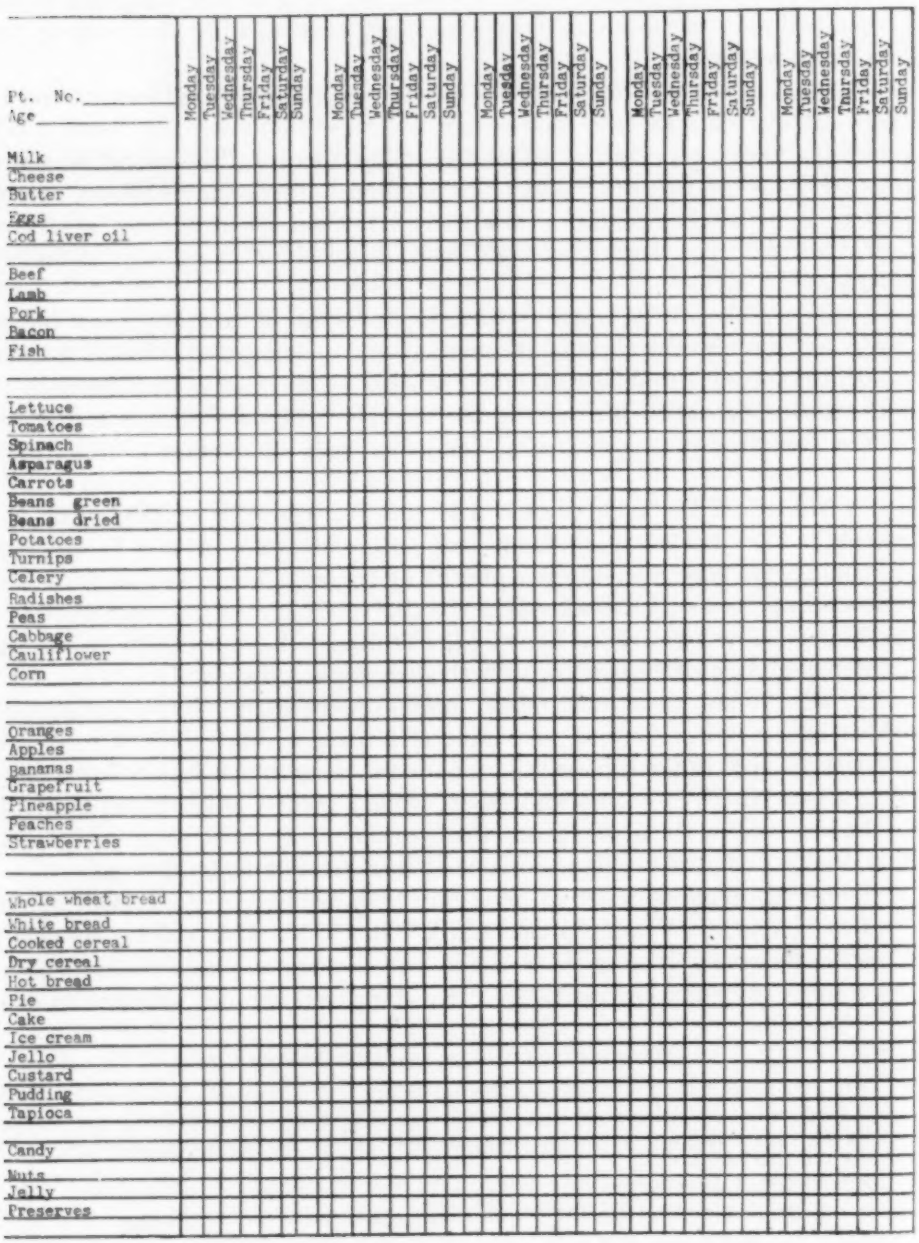
Pt. No.
Age
Monday
Tuesday
Wednesday
Thursday
Friday
Saturday
Sunday
Milk
Cheese
Butter
Eggs
Cod liver oil
Beef
Lamb
Pork
Bacon
Fish
Lettuce
Tomatoes
Spinach
Asparagus
Carrots
Beans green
Beans dried
Potatoes
Turnips
Celery
Radishes
Peas
Cabbage
Cauliflower
Corn
Oranges
Apples
Bananas
Grapefruit
Pineapple
Peaches
Strawberries
Whole wheat bread
White bread
Cooked cereal
Dry cereal
Hot bread
Pie
Cake
Ice cream
Jello
Custard
Pudding
Tapioca
Candy
Nuts
Jelly
Preserves

CHART 1.

It is significant that the average number in the families of 75 rheumatic patients was 7.5 members per family, whereas the average family group in the middle class runs 4.5 members per family. It is obvious that the family with twice as many to feed on the same amount of income must of necessity buy the cheaper foods which all too often are the starchy foods. However, this survey has shown that the economic state is not the sole problem, for we have some people with an adequate income who are living on the impoverished diet. The problem in this instance is one of education and of change in the individual's dietary habits.

Those people who take full advantage of the sunshine and whose diet is rich in minerals, with a proper calcium-phosphorus ratio, or those who substitute for the sunshine a liberal amount of the fats that are rich in natural

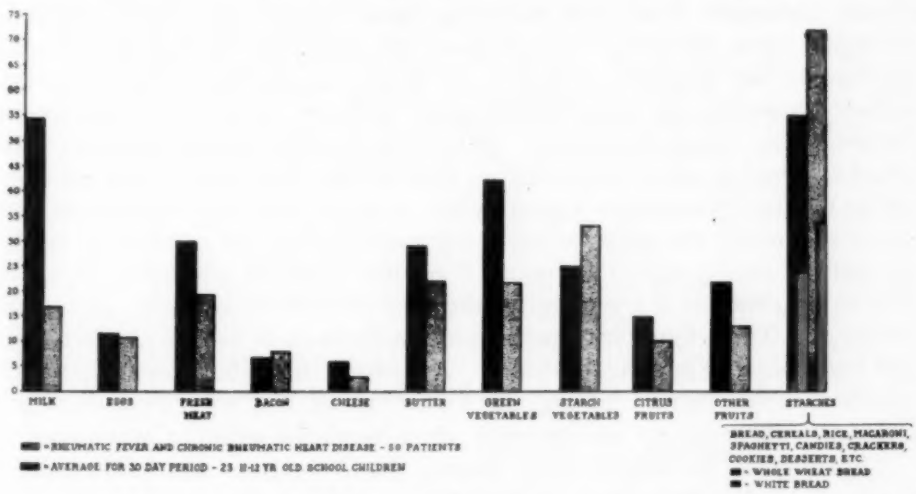

CHART 2. These figures indicate the average times per month that a group of 50 patients with acute rheumatic fever and rheumatic heart disease ate the above foods. They are compared with 25 average, normal school children.

sources of vitamins A and D have a low incidence of rheumatic fever and its sequelae. This fact is emphasized by the rarity of rickets and dental caries among the primitive Eskimo tribes who live upon a high protein diet made up largely of fish and oils. The mothers nurse their babies until the teeth erupt because the child must be able to chew the meat which is a large part of his very earliest diet. Those tribes which have changed their habits of eating to include flour, sugar and other starches show severe rickets, scurvy, and dental caries and rheumatic disease.[12, 13, 25] It is of particular significance that Harrington,[26] in his experience in Charleston, South Carolina, found a very low incidence of rheumatic infection among those people whose occupation was primarily fishing, and conversely, a high incidence among the workers in the industrial and rural districts. The experience of John Schmidt,[47] as a medical missionary in several colonies in Paraguay, South

America, is noteworthy. During a 15 months' stay he examined 1300 people and found only three with rheumatic fever, two boys five and eight years of age and a girl 14. These people have an abundance of milk, eggs, butter, cheese and meat. Lettuce, green beans and potatoes are plentiful but other vegetables are scarce as is wheat flour.

The findings of Heinbecker and Irvine-Jones,[27] following their immunologic studies among the Eskimos, substantiate the theory that dietary factors influence immunologic reactions. Their work shows that after the age of 12 the Eskimos, living as a primitive people far away from scarlet fever, diphtheria and rheumatic fever, are immune to scarlet fever and diphtheria and showed only mildly positive skin reactions, in a small number of cases, to filtrates from rheumatic fever.

In 1938 Stott [1] published convincing evidence to show that in a tropical climate rheumatic fever and rheumatic heart disease are fairly common, averaging about six cases of acute rheumatic infection for every 1,000 admissions to the hospitals of India. It is also interesting to note that the highest admission rate occurred during the cold, dry months and not during the hot, damp, monsoon months. Mitra,[28] in the same medical journal, published evidence to show that many of these Indian communities live on diets low in calcium, phosphorus and proteins; some are not only vegetarians, but it was also found that they did not compensate for the lack of meat by drinking milk or eating eggs. Fernando [29] reports from the hospitals of Ceylon that an incidence of 2.2 per cent of the total admissions is due to rheumatic infection. These figures compare closely with those figures of the five general hospitals in Victoria, Australia. Nicholls,[30] in 1936, showed that malnutrition is widespread among the lower classes and that their diets are deficient both in quality and quantity when compared with the upper classes.

A study of rheumatic fever among the Aborigines in Australia and among the Indian tribes in the United States [32] reveals that the disease occurs among these the same as it does in other races in the same climate. Studies in Australia and in England point out that although the incidence of rheumatic fever is much higher among the poorer class, it is the middle-class poor, rather than the very poor who are on relief, who suffer most. This would suggest that those on relief are living on better diets since they may not choose the "tasty" foods but must accept that which is given to them. These studies in Australia refute the common belief that dampness is an important etiologic factor. Hedley's [33] surveys also indicate that the disease is one of poverty rather than one of climate. Paul,[34] at New Haven, Connecticut, and Coombs, [35] in Bristol, England, found that the amount of rheumatic fever was lowest in private schools, higher in the rural schools and highest in the city public schools. These findings indicate that there must be something in the individual's living habits that will protect him or predispose him to the infection. Whereas reports from Mexico,[9] England,[14, 15, 16, 17] Holland,[36] Costa Rica,[8] Hawaii,[11] India,[1, 2, 3] Australia,[4, 5, 6, 7] Argentina,[10] and from

various states in the United States [18] indicate that rheumatic fever and rheumatic heart disease are found in nearly every country in the world except among the native, primitive Eskimos, the incidence of the disease usually is seen to vary with the climatic conditions.

During the 30 year period, 1910 to 1940, there was a general downward trend in the death rate due to rheumatic fever in the United States as shown

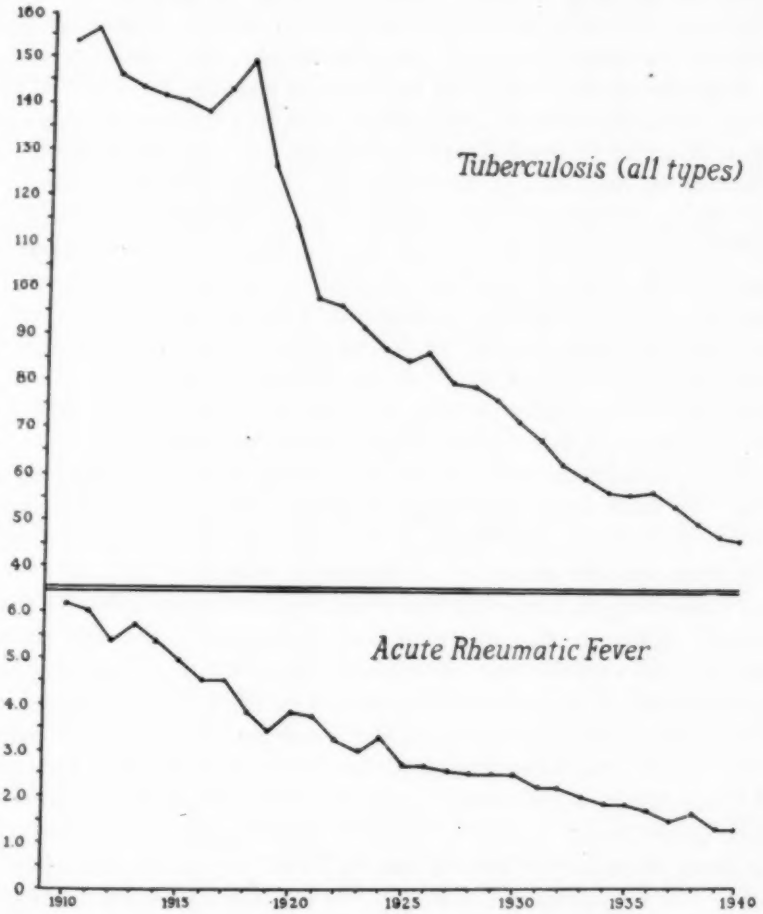

CHART 3. Graph, comparing rheumatic fever and tuberculosis, shows a decline of death rates per 100,000 population.

in the graph. This decrease in death rate has been noted in Australia and England also. A similar trend is shown in the graph relating to tuberculosis. It is believed that this reduction is the result of three very important factors which will require continued emphasis if this improvement is to progress. First, there must be adequate food available at a price the masses can afford; second, people must be educated to the importance of an adequate diet, and

the value of sun bathing; third, the necessity for early medical care with complete bed rest until all signs of activity have subsided.

In table 1, which is taken from the Vital Statistics of the Department of Commerce—Special Reports, 1940—is shown the death rate due to acute rheumatic fever and chronic rheumatic heart disease during 1940 for each 100,000 population and also the actual number of deaths for each state. The death rate for pellagra is also shown. In order to indicate the amount of dairy products available throughout the United States, an attempt was made to determine the number of cows per population. No statistics were available to demonstrate this important fact; it was possible, however, to show the percentage of farms without cows and pigs, so this information was included in table 1, in order to demonstrate, generally, the relation between the food available and the incidence of rheumatic disease and pellagra, which is known to be a deficiency disease.* The death rate for pellagra would indicate that the problem of adequate diet is far from solved in our own country. In studying these figures one sees that many of our southern states have a higher incidence of rheumatic diseases than some of the more northern states. The answer to this is found, we believe, in the type of crops that are raised in the different sections of the country. In the South, where cotton is king, or in the industrial centers where the crop or labor is exchanged for money, the individual in turn buys those foods which are the most pleasing and which are the cheapest; usually these foods are the starchy ones, with meat in deficient amounts. In table 1 the percentage of farms without cows and hogs in the United States is shown and one sees that there is some relation between the food available and the incidence of rheumatic infection.

It is interesting to note that there was a great acceleration in the downward trend of the death rate from both rheumatic fever and tuberculosis after the discovery of the true cause of rickets by Findlay,[37] in 1908, and following Mellanby's [38] experiments on rickets in 1918. It is possible that the preventive measures taken to lower the incidence of rickets, in addition to the public health measures instituted to control tuberculosis, have been responsible for much of this lowering of the death rate from rheumatic fever. To show better many common features of rheumatic fever and rickets I wish to quote from an excellent review by Park [39] upon the etiology of rickets in 1923: *"The Occurrence of Rickets.* It is a disease found in cities. It is most prevalent in those nations whose wealth and industrial development have brought about most fully the substitution of artificial conditions of living in place of the simple conditions which nature intended. Wherever civilization of this artificial character establishes new contacts, rickets begins to appear. The disease has appeared in India where the designs of nature have been interfered with by religious customs to be mentioned later. The disease never occurs among peoples living under natural conditions. Savages may starve and may become the victims of pestilence, but they do not develop

*We do not believe that vitamin B deficiency is a predisposing factor to rheumatic fever.

TABLE I

Statistics

States	Vital Statistics			Percentage of Farms without cows and hogs		Death Rates (no. per 100,000 enumerated population)	
	Deaths from selected causes in the United States (1940) Dept. of Commerce Reports			Bureau of Agricultural Economics			
	Acute Rheumatic Fever	Chronic Rheumatic Disease of the Heart	Pellagra (except alcoholics)	% Farms without milch cows	% Farms without hogs and pigs (1939)	Acute Rheumatic Fever	Chronic Rheumatic Disease of the Heart
New England:							
Maine	11	212	—	28.6	72.5	1.3	25.0
New Hampshire	5	129	—	34.6	82.4	1.0	26.2
Vermont	2	110	—	18.9	78.5	0.6	30.6
Massachusetts	30	1,142	6	49.4	89.5	0.7	26.5
Rhode Island	3	156	1	39.6	88.0	0.4	21.9
Connecticut	24	337	3	38.9	91.0	1.4	19.7
Middle Atlantic:							
New York	177	3,478	18	24.4	72.9	1.3	25.8
New Jersey	77	913	9	51.2	79.1	1.9	21.9
Pennsylvania	172	2,263	17	25.8	51.1	1.7	22.9
East North Central:							
Ohio	98	1,612	9	20.0	38.2	1.4	23.3
Indiana	39	780	10	16.8	27.3	1.1	22.8
Illinois	96	1,791	20	13.7	24.1	1.2	22.7
Michigan	45	1,058	10	22.4	52.7	0.9	20.1
Wisconsin	53	589	3	10.4	41.1	1.7	18.8
West North Central:							
Minnesota	41	569	5	12.2	31.8	1.5	20.4
Iowa	27	600	3	10.0	14.9	1.1	23.6
Missouri	39	1,157	13	15.8	23.8	1.0	30.6
North Dakota	14	79	2	16.4	38.6	2.2	12.3
South Dakota	11	87	1	16.7	31.3	1.7	13.5
Nebraska	9	268	2	13.7	31.7	0.7	20.4
Kansas	9	393	6	17.3	46.5	0.5	21.8
South Atlantic:							
Delaware	5	70	—	38.1	46.2	1.9	26.3
Maryland	35	473	7	34.5	45.3	1.9	26.0
Dist. of Columbia	10	133	1	—	—	1.5	20.1
Virginia	49	543	59	24.2	34.1	1.8	20.3
West Virginia	24	274	11	19.6	41.6	1.3	14.4
North Carolina	68	522	169	35.3	31.1	1.9	14.6
South Carolina	42	314	161	36.2	24.2	2.2	16.5
Georgia	46	381	251	26.6	23.7	1.5	12.2
Florida	30	360	72	56.7	48.4	1.6	19.0
East South Central:							
Kentucky	41	515	60	19.0	35.3	1.4	18.1
Tennessee	70	628	102	21.2	29.7	2.4	21.5
Alabama	48	526	244	21.6	25.7	1.7	18.6
Mississippi	32	476	169	34.1	27.3	1.5	21.8
West South Central:							
Arkansas	24	237	104	25.8	31.4	1.2	12.2
Louisiana	20	450	75	30.9	27.3	0.8	19.0
Oklahoma	25	330	61	14.6	35.2	1.1	14.1
Texas	68	634	354	19.1	39.6	1.1	9.9
Mountain:							
Montana	5	121	1	29.5	60.8	0.9	21.6
Idaho	9	99	3	18.3	42.5	1.7	18.9
Wyoming	3	40	—	21.0	56.0	1.2	16.0
Colorado	11	257	1	26.5	52.4	1.0	22.9
New Mexico	8	67	19	46.6	61.6	1.5	12.6
Arizona	5	55	5	62.8	86.0	1.0	11.0
Utah	10	153	3	22.2	47.3	1.8	27.8
Nevada	—	22	1	34.1	60.1	0	20.0
Pacific:							
Washington	12	410	5	29.1	70.3	0.7	23.6
Oregon	11	280	4	24.6	63.4	1.0	25.7
California	32	1,337	43	61.0	84.9	0.5	19.4

rickets. The disease does not occur in the native parts of Africa and is exceedingly rare in China and Japan. It occurs rarely in the tropics, and is rare in the Arctic regions. . . . The seasonal variation in rickets was beautifully demonstrated in the pathological studies of Schmorl. These studies showed that rickets may begin at any time, but the highest percentage of early manifestations of the disease is between November and May. The percentage of cases with signs of healing increased as the summer progressed and reached its highest point in the autumn, only to fall again as the winter months came." The many different theories that were advanced concerning the cause of rickets were not unlike the many theories discussed as the cause of rheumatic fever.

For some time we have been impressed with the more severe form of rheumatic fever among the Negro and Mexican children. This fact has been recognized by Hedley,[33] and Ash.[40] Boas [41] has pointed out the severity of rheumatic carditis in the adult Puerto Rican immigrants in New York City. We have explained this difference in severity and incidence among those people with dark skins as being the result of their inability to take advantage of the reduced amount of actinic rays in a more northern climate than that to which they are accustomed. This difference was noted among those having rickets. Park [39] states: "A study was made by Hess and Unger of the diets of the negro mother in a negro district of New York City where rickets was exceedingly prevalent among breast-fed children. The negroes were, for the most part, immigrants from the West Indies where they lived chiefly on meat or fish, rice and potatoes, tea, coffee and cereal. Milk was taken in small quantity and fruit rarely. The vegetables, which were taken in small amounts, were usually canned. In New York City the women lived indoor lives. The striking points brought out in the study were that the mothers had exchanged an outdoor life in the tropics for an indoor life in the temperate zone and a dietary in which green vegetables and green leaves figured largely for one in which those articles of food were almost entirely lacking."

This similarity between rheumatic fever and rickets is manifested not only in the incidence socially and by geographic distribution, but there is also a close relation between the tissues involved in the two diseases. Rheumatic fever involves primarily the mesodermal or the connective tissue structures of the body, whereas rickets is a disease involving the cartilage and the bone, which is, of course, derived from the connective tissue. Both of these diseases usually have a secondary anemia and the individuals are generally underweight. These facts certainly suggest the possibility that a deficiency in vitamin D from a lack of sunshine, when not compensated by vitamin D in the diet, and associated with diets too low in calcium and phosphorus, effects a change in the immune forces of the individual. It is not at all unlikely that vitamin D is very essential in the normal development of all mesodermal structures. We know that it is stored in the fat cells, which are a modified form of connective tissue cell, and we know also that it is found

most often stored in the liver. Cannon,[42] in a recent discussion of antibodies and the protein reserves, states that: "Antibodies are substances which, after intracellular formation, are excreted or secreted into the blood or lymph. The accumulated evidence of 50 years leaves little doubt but that the macrophage (broadly defined) is the principal cell concerned with their production. This does not exclude the possibility, however, that other types of cells may also participate to some extent either in synthesis of antibodies or in the development of the antibody mechanism." In his paper Cannon clearly emphasizes the importance of protein in antibody production.

Another fact to be noted about the macrophage system, which has become known as the reticuloendothelial system, is that it is made up of cells that have the ability to take up particulate matter and to store foreign substances brought to them in colloidal solution.[43] The macrophage system or the reticuloendothelial system is derived from mesodermal tissue, the same tissue from which bone and connective tissue are derived. These facts also lead me to believe that vitamin D may be necessary in the normal development of all mesodermal structures. If this theory is true, it could account for the infection being so much more common in childhood during the developmental period. This could be the answer to the statement made by Coburn [44] in 1932: "The collected observations on the relation of the activity of the rheumatic process to hemolytic streptococcus, and the failure to detect a single serological type of organism associated only with rheumatic fever, have led to the conception that the specificity of the rheumatic response, like the reaction in certain other streptococcus diseases, depends not entirely upon the character of the parasite but is perhaps related to some individual mechanism of the rheumatic subject." This theory could explain also the reason for the statement of Swift,[45] in 1940: ". . . crowding, poor housing and poor nutrition seem to play almost as important unfavorable rôles in hot as in cold climates."

A most recent study of the epidemiology of juvenile rheumatism in the British Isles, by Morris and Titmuss,[17] led to these conclusions: "Mortality on the whole increases with the density of population; this seems to be a function of the greater poverty in towns. The depressed rural districts return rates as high as the worst of the big towns. No evidence was found to suggest that the artisan stratum is particularly prone to the disease. Climate seems of little importance. Correlation with overcrowding was inconclusive. The facts elucidated strengthen the view that the whole complex of poverty is involved in the production of juvenile rheumatism."

Because of these facts, patients have been studied recently with a consideration of signs of previous disturbances in the mineral metabolism, i.e., dental caries, scoliosis, flaring of the ribs, or thoracic deformities known to be acquired, bow legs and knock knees. This study has been very interesting, for we find many of our patients show at least one of these signs, and some show evidence of several such disturbances. This fact, coupled with

the result of a dietary survey showing foods inadequate in calcium, phosphorus and vitamins A and D, and too high a ratio of carbohydrates, has suggested the feasibility of treatment with high potency vitamins A and D * and an increase in calcium and phosphorus values in the diet. Preliminary studies in a small series of patients so treated are promising and warrant continuation of the experiment on a large scale.

The following evidence indicates that diet and sunshine are the most important predisposing factors in the causation of acute rheumatic fever:

(*a*) The incidence of acute rheumatic fever and rheumatic heart disease increases as exposure to the sun decreases.

(*b*) Very low incidence of rheumatic infection exists in those countries which have an abundance of proteins and fish oils in the diet.

(*c*) The incidence of rheumatic infection is lowest in the private schools, next lowest in the rural schools and highest in the public schools.[34, 35]

(*d*) Poverty, and not dampness, is the predisposing factor.[33, 4, 17]

(*e*) Holland, with a cold, damp climate, shows a low incidence of rheumatic heart disease.[36]

(*f*) Those states in the United States which are primarily farm and dairy states have a lower incidence of the infection than those states which are largely industrial, or whose chief crops are cotton, tobacco and similar produce.

(*g*) A study of 76 patients with rheumatic heart disease and acute rheumatic fever reveals that the average size family is 7.5 persons per family. This indicates that persons in low income groups with large families have to spread the milk, butter, eggs, meat and fresh vegetables "too thin."

(*h*) There have been very few recurrences of active infection when families have coöperated in the correction of diets and in the addition of cod liver oil to the diet.

(*i*) Studies of the vital statistics, 1910 to 1940, show that the death rate for rheumatic fever follows the same tendency as that of tuberculosis, namely, a downward trend with improvement in economic conditions and education. Both of these diseases are primarily diseases of poverty.

(*j*) Poor dietary habits have been found to exist among those with adequate financial means. This condition was revealed by our method of dietary survey, using chart 1.

(*k*) Those races having much skin coloring are more susceptible to rheumatic fever when taken to climates having less sunshine than that to which they are accustomed; they also have a more virulent form of the disease.

(*l*) Seasonal variation is noted in the incidence of the disease, being more common in the winter and spring, following a period of inability to benefit from exposure to the sun.

* Vitamin A 25,000 units and vitamin D 50,000 unit capsules were supplied by Brewer and Company.

(*m*) Those people who live in high altitudes, because of cold climate and a consequent lack of body exposure to the sun, have a higher incidence of rheumatic infection when they do not compensate for these deficiencies by increased quantities of vitamin D.

(*n*) Immunologic studies among the Eskimos show that there is a natural immunity after the age of 12 to scarlet fever, diphtheria and also to filtrates from rheumatic fever patients.[27]

Finally, it is my belief that this deficiency, which closely follows the incidence of clinical rickets, alters the individual's immunity to the infective organism that produces the clinical picture of acute rheumatic fever. The importance of adequate amounts of vitamins A and D, milk, protein and the value of sun bathing cannot be overemphasized in the prevention of this crippling disease and its recurrences.

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SHORT P–R INTERVAL ASSOCIATED WITH PROLONGATION OF QRS COMPLEX; A CLINICAL STUDY DEMONSTRATING INTERESTING VARIATIONS *

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Because of the recent interest in the syndrome of the short P–R interval associated with a prolonged QRS complex, without organic heart disease (Wolff-Parkinson-White syndrome), as evinced by the publication of several articles on this subject in the past two years, it is desired to add four other cases to the rapidly growing list of reports. In accordance with the sex predominance previously reported [1] all of these have occurred in healthy, young male subjects. Other characteristics include absence of definite organic heart disease, slurring of the initial ventricular deflection, a peculiar susceptibility to attacks of paroxysmal tachycardia, either supraventricular or ventricular in type, and reversal to normal electrocardiographic pattern either spontaneously or after exercise or after atropine administration. Use of this drug resulted in reversion to a normal type of tracing in one of our cases; there was no appreciable effect in two; and in the remaining one a "paradoxical" effect was demonstrated. Marked T-wave variations have also been seen, especially in the limb leads, both spontaneously and after atropine.

In 1937 Bishop [2] reviewed the literature, and two years ago Hunter, Papp and Parkinson [3] enumerated the various ingenious mechanisms advanced to explain this phenomenon. The most plausible and generally accepted explanation is that proposed by Wolferth and Wood,[4] namely ventricular asynchronism due to the premature stimulation of one ventricle through an abnormal conducting pathway. These authors, in their most recent communication,[5] have stated their reasons in support of such an hypothesis, and offer experimental evidence in its behalf. Our prime purpose in presenting these cases is to report our observations of the electrocardiographic changes noted, with particular reference to the variations in the terminal ventricular complex.

Case Reports

Case 1. On July 15, 1942, one month after his induction, F. L. G., a slightly undernourished but well developed white male adult, 24 years of age, was admitted to the Station Hospital because of dermatitis venenata. His father died at 52 years of age of an acute cardiac episode, and his mother died at the age of 40 of diabetes. Of seven siblings, five are living and well, one is said to have valvular heart disease, and one died at the age of 42 of an acute cardiac condition. His past history re-

* Received for publication March 27, 1943.

vealed the usual infectious diseases and pneumonia as a child. No history of diphtheria, scarlet fever, or any of the rheumatic manifestations could be obtained. At 20 years of age he had a cyst (reported to be of sebaceous type) removed surgically from the anterior surface of his neck. He always felt weak and undernourished and could never do any hard work. For the past five years, after exercise, his heart would beat fast and he would "get pains around his heart" and shortness of breath. At times his heart would "run away." Even while at rest his heart would take a sudden jump, and he felt as "though the blood flowed fast through it." At times, also, he could feel his heart beating very rapidly to the left and below his left nipple.

There was no history of venereal infection or serious injury. He smoked one pack of cigarettes daily; no alcohol or drugs were used.

Physical examination revealed an apparently well male adult 6 feet 5 inches tall, weighing 124.5 pounds. There was a diffuse papular rash over both forearms and axillae, and both legs. He showed a well healed vertical scar in the midline of his neck just over the thyroid cartilage. The examination was otherwise not remarkable except for a mild tachycardia, rate 108, and a fine tremor of the outstretched hands. Blood pressure was 114 mm. Hg systolic and 70 mm. diastolic.

Laboratory data: Urinalysis was normal chemically and microscopically. Blood —red blood cells 5.35 M., hemoglobin 17.5 gm., white blood cells 7,700. Differential formula: polymorphonuclears 68, lymphocytes 27, monocytes 5. Fasting blood sugar was 131 mg. Blood cholesterol 223 and 221 mg. Basal metabolic rates were reported plus 37 and plus 36. Following medication with phenobarbital gr. one three times daily, rechecks were obtained and reported minus 8 and plus 4.

Roentgenogram of the chest revealed a heart of normal configuration and no lung disease.

Electrocardiogram (figure 1–a) on admission showed a tracing resembling left bundle branch block of the discordant type. It showed a regular rhythm with a rate of 85, a P–R interval which varied between .10 and .12 and a QRS width of .11. T_1 was inverted, and in Lead IV–F there was an absent S-wave with slightly elevated RT segment. The ascending limb of R_1 arose from the P-wave before the latter had returned to the base line. The initial ventricular deflection was slurred in all leads.

In order to test the effect of atropine on our first patient he was given the drug in doses of gr. 1/100 every four hours until he complained of dry mouth and blurring of vision, and showed dilated pupils. A tracing at this time showed, paradoxically, a marked respiratory arrhythmia and bradycardia (figure 1–b). The rate was slowed to slightly less than 60, the P–R interval increased to .13 and the width of the QRS was shortened to .08. These values varied somewhat in the different leads but for the sake of uniformity, Lead II was used for their determination. However, the most interesting changes occurred in the terminal ventricular complexes. T_1 which had previously been inverted now became upright, T_2 closely resembled the "coronary T", and $T_{4\text{-}F}$ became much taller and slightly wider. A few minutes later a tracing was taken following exercise. The only discernible change was an increase in rate. Evidences of the arrhythmia persisted. Exercise alone, without the added effect of atropine, had previously caused T_1 to become upright without any other demonstrable change. The tracing immediately following the ingestion of 300 c.c. of ice water showed only a mildly diphasic T_1. The effects of changes in posture consisted mainly in alteration of the T-wave. T_1 which was inverted while in the supine position became practically isoelectric while sitting, and only slightly inverted while standing. T_2 was essentially unchanged. T_3, which was upright and well marked in the supine position, became of low voltage while sitting and was barely discernible while standing. T_4 was unchanged.

Case 2. W. M. M., a well nourished and developed adult colored male, 24 years

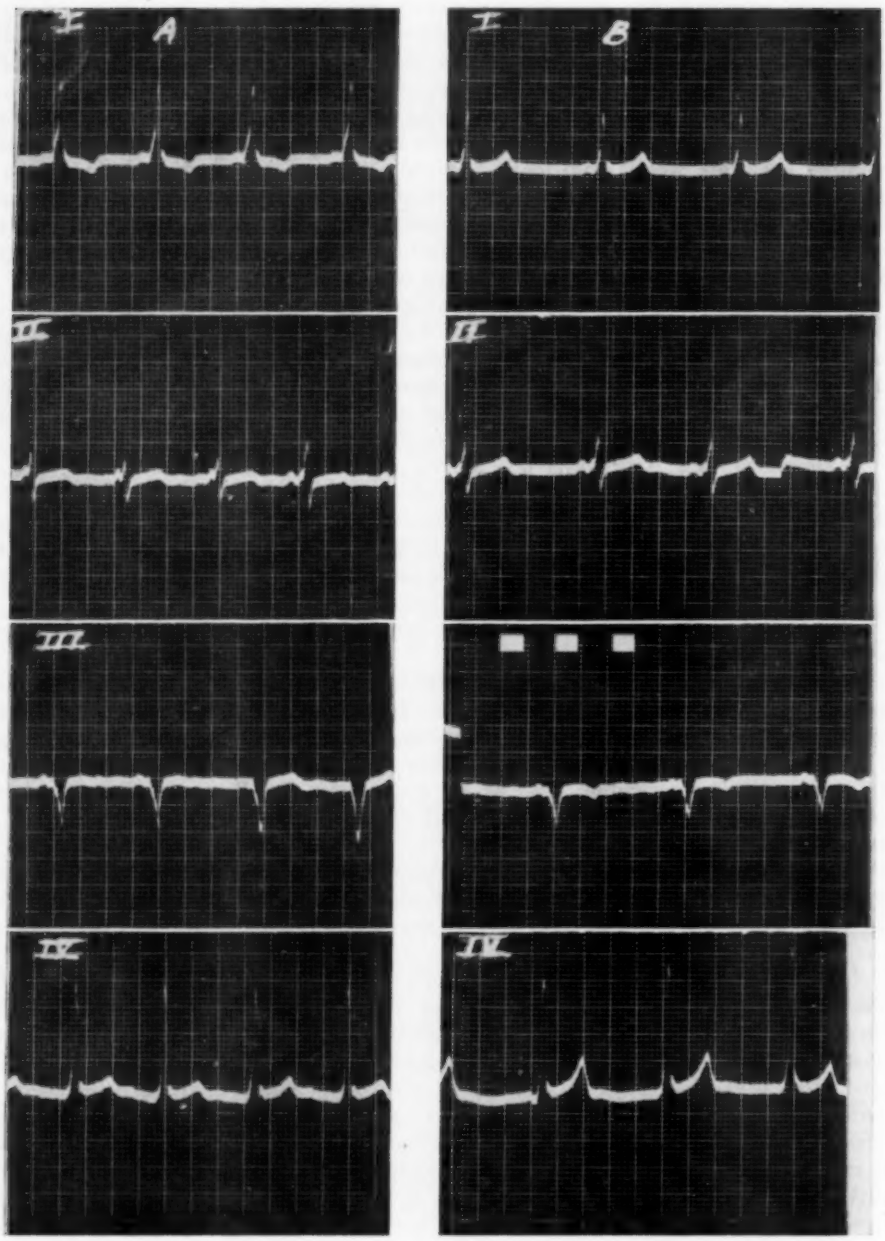

FIG. 1. *Case 1.* A—original electrocardiogram; B—after atropine. Note bradycardia, respiratory arrhythmia, and alterations of T-waves.

of age, was admitted on October 10, 1942, because of paroxysmal tachycardia. He was of normal habits with negative past and family history. For the preceding three years he had had attacks of rapid heart action about twice weekly lasting two to three minutes. During these episodes precordial pain and dyspnea were noted. On

the morning of October 10, while doing field exercises, he experienced one of his attacks, and his pulse rate at that time was about 200. This was witnessed by the dispensary medical officer. By the time he had reached the hospital the tachycardia had subsided, his pulse and heart rates being 78. Physical examination was essentially normal. There was no cardiac enlargement, nor were there any murmurs or thrills. The only positive finding was a chronic laryngitis. The Kahn reaction was negative, and urine and blood counts were within normal limits. An electrocardiogram taken on October 12, 1942 (figure 2–a) showed a tracing resembling left bundle branch block of the discordant type. There was sinus arrhythmia and bradycardia with a P–R interval of .08 to .09 second and the QRS duration was .12 to .14 second in different leads. The initial ventricular deflection was slurred in all leads, and as in the first case, arose from the P-waves before the latter had reached the base line. All T-waves were upright. This patient was also atropinized up to tolerance, but the only significant change observed (figure 2–b) was inversion of T_3 so that it simulated the coronary T-wave. The heart rate was also slightly increased.

Case 3. Sgt. W. R. J., white, age 20 years, was admitted to the hospital on December 17, 1942, with the complaints of tachycardia, dyspnea, and irregular heart action. These symptoms had been noted after exertion for a period of two years, but it was stated that, during recent months, the frequency and severity of attacks had been increasing and followed less strenuous exercise. The cardiac symptoms had usually lasted from five to 10 minutes and were sometimes associated with "blind spells," although syncope had not occurred. Precordial pain had not been noted at any time. Carotid sinus pressure had not produced cessation of tachycardia, but the patient thought that holding the breath had hastened relief.

Prior to induction the patient had been a student. He had completed two years of military service, his work being operation and maintenance of teletype apparatus. Symptoms were first noted shortly after his induction into the service.

Past medical history revealed nothing of importance, and family history showed no incidence of cardiac disease in parents or six siblings. Habits had been normal, with very moderate use of tobacco and alcohol.

The soldier was 73 inches in height, and his weight was 164 pounds. Aside from the cardiovascular system the physical examination revealed entirely normal findings, and laboratory examinations afforded nothing of interest. The heart presented no enlargement and there was no irregularity. The rate at rest was 100 per minute, increased to 136 on mild exercise, and returned to 102 after two minutes of rest. With the accelerated rate after exercise the apical first sound was accentuated, but no murmurs were heard at any time. No thrill was present. The blood pressure varied from 142 mm. Hg systolic and 96 mm. diastolic, on admission, to 108 mm. Hg systolic and 68 mm. diastolic on later determinations.

On the day after admission an electrocardiogram (figure 3–a) revealed auricular and ventricular rates of 70 per minute. The P–R interval varied from .08 to .11 second in different leads. The QRS complexes measured .12 to .14 second, with the features of left bundle branch block of the discordant type. As in the other cases, the initial ventricular deflection was slurred. The RS–T segments were slurred in all leads. The T-waves in Lead I were diphasic, but upright and peaked in Leads II and III. In Lead IV–F the T-waves were sharply inverted.

After hypodermic administration of three doses of atropine sulphate, each gr. 1/150, at intervals of four hours a second electrocardiogram was made. No appreciable change was noted. Six days later cardiograms were made before (figure 3–b) and after exercise. Both of these tracings revealed normal sinus rhythm. The P–R interval measured .16 second. QRS was diphasic in Lead I, upright in Leads II and III, with a duration .08 second. Marked differences were noted in the T-waves of this and the preceding tracings. T_1 was now definitely upright instead of diphasic;

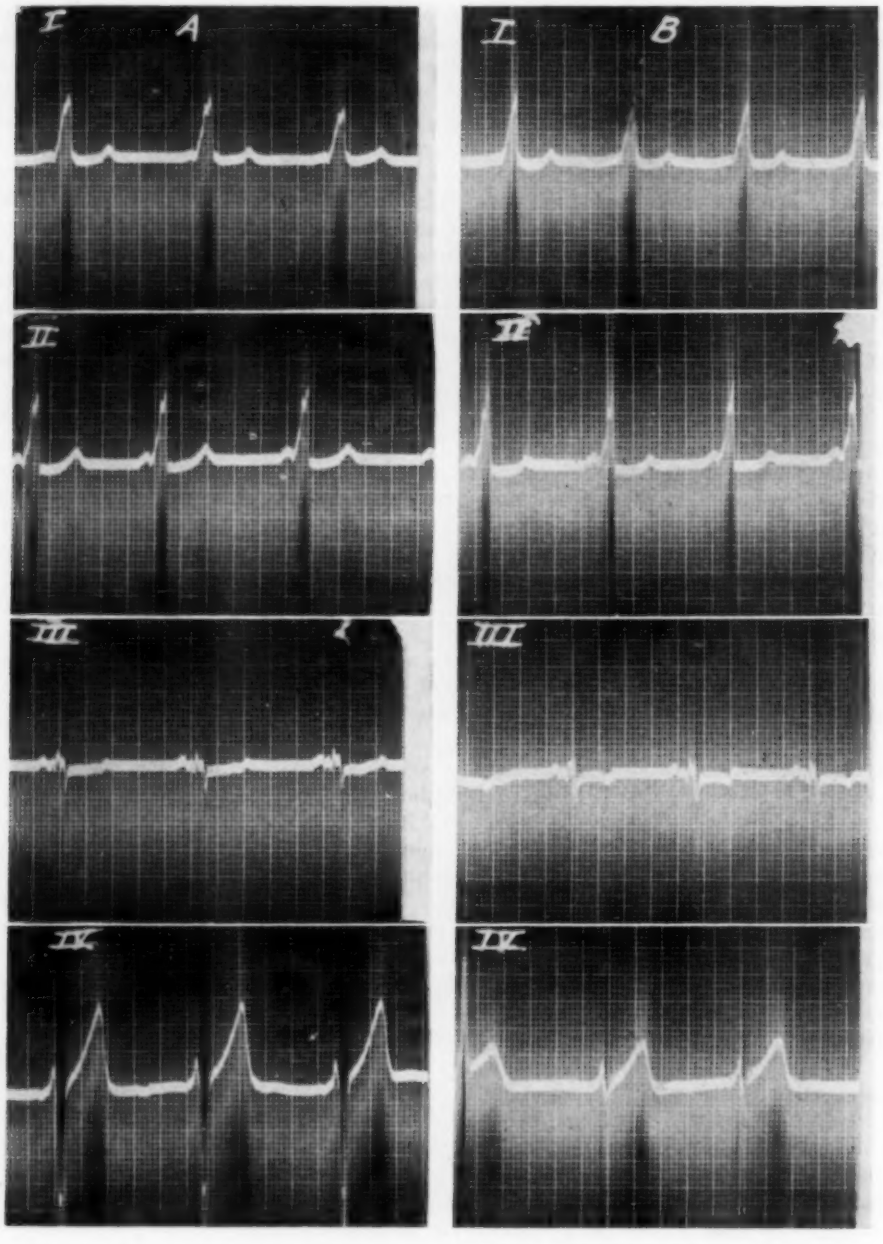

FIG. 2. *Case 2.* A—original; B—after atropine. T_3 and T_4F show alterations.

T_2 remained upright but of reduced amplitude; and T_3 instead of being upright was sharply inverted. The QRS complex in Lead IV–F instead of being entirely upright was now diphasic, and T_4 was now upright rather than inverted. The tracing obtained after exercise was identical with that at rest except for the expected acceleration in rate.

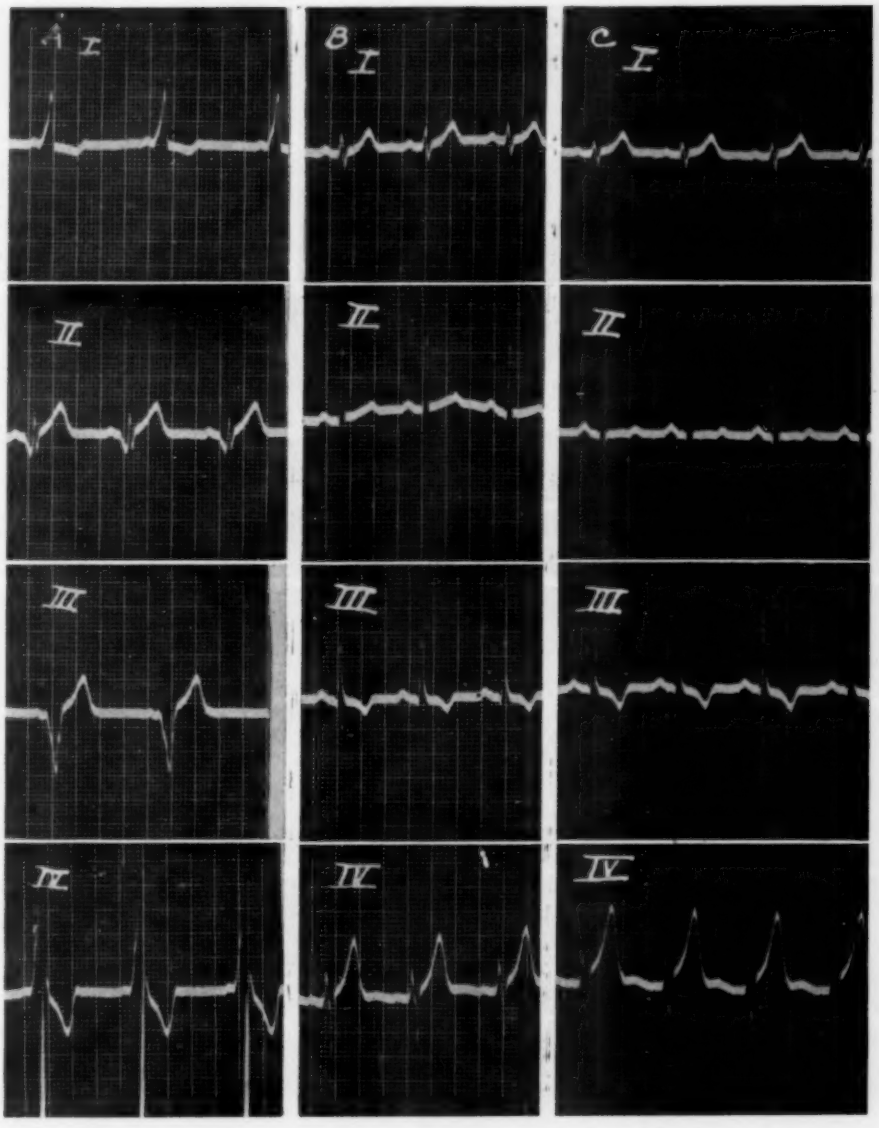

FIG. 3. *Case 3.* A—original; B—showing spontaneous reversion to normal sinus mechanism; C—sinus rhythm after administration of atropine. Alteration of T-wave is evident in all leads, in both spontaneous and induced reversion.

Electrocardiograms were made at intervals of several days, and in each instance the pattern was the same as on the original examination.

Atropinization with the previously used dosage was repeated, with similar negative result. On another day, after a control tracing to establish the presence at that time of the short P–R interval and prolonged QRS complex, atropinization was carried to the limit of tolerance. In a period of four hours and 40 minutes 1/25 grain was administered by hypodermic in divided doses, in addition to 2/100 grain orally.

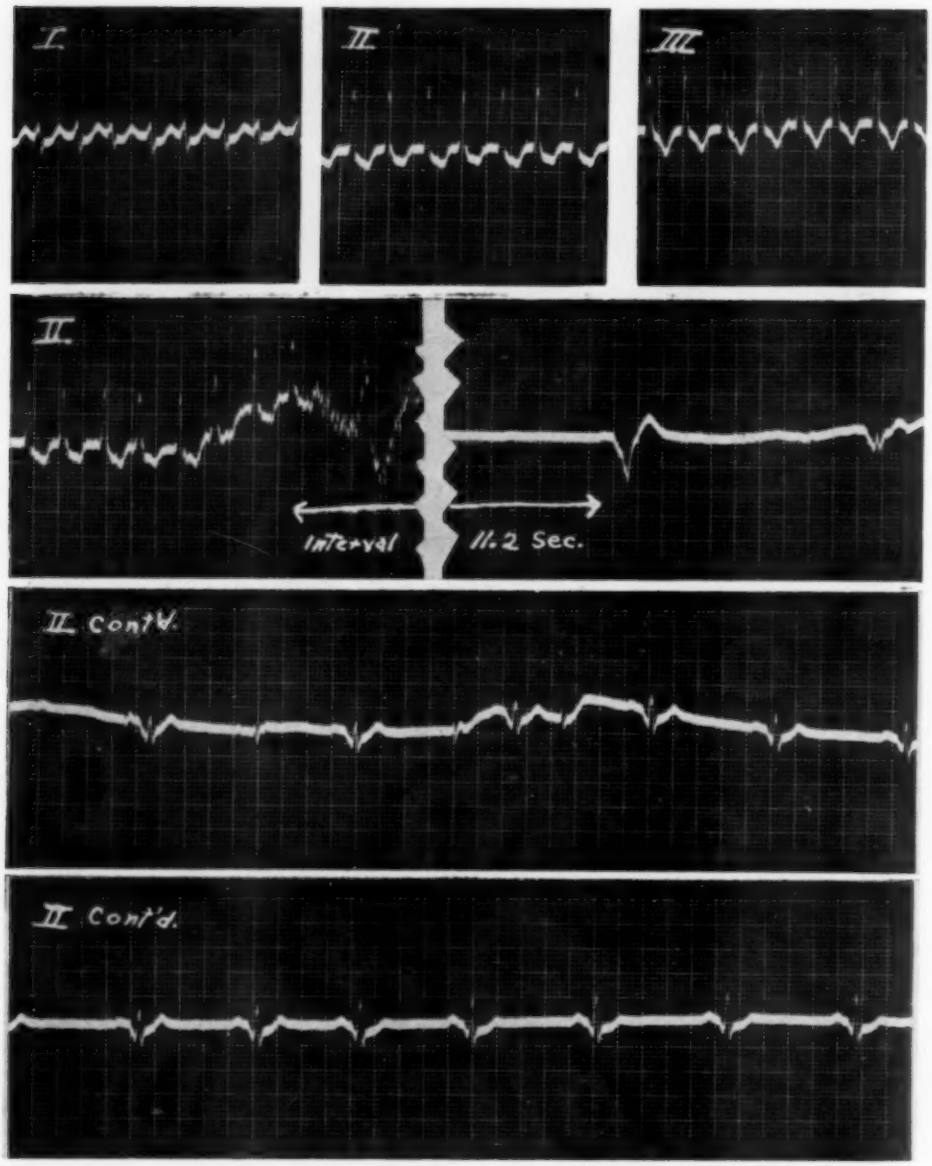

FIG. 4. *Case 3.* Cessation of tachycardia after ocular pressure. Limb leads above. Lower three strips, except as indicated, are continuous.

Within 30 minutes after the last medication an electrocardiogram was made (figure 3-c). This tracing was identical with that obtained when spontaneous reversion to normal rhythm occurred.

A fast run of 150 yards precipitated an attack of tachycardia of supraventricular type (figure 4). Cessation of the tachycardia was brought about by ocular pressure. Following initial deflections of the beam during pressure there was a period of

asystole which persisted for 11.2 seconds. Cardiac action was resumed with complexes which were irregular both in time and in contour, gradually returning to the characteristic short P–R and prolonged QRS pattern.

Case 4. Pvt. J. W., a 36 year old colored soldier with one month of military service, was hospitalized on November 24, 1942. He stated that difficulty was first noted in May, 1940 when he awakened from sleep with palpitation, tachycardia, a choking sensation and precordial oppression. Similar attacks recurred at intervals, with one in September, 1941 more severe than the others, after which bed rest was advised for four months. More recent attacks had been associated with dyspnea, but precordial oppression was noted only if the tachycardia followed exertion.

Past history revealed no illness of note, and venereal infections were denied. Father, mother, and five siblings were alive and well, and there was no incidence of cardiac disease.

Physical examination revealed a good state of development and nutrition. There was definite clubbing of the fingers. The blood pressure was 120 mm. Hg systolic and 90 mm. diastolic. The cardiac rate was 80 per minute, and regular. There were no thrills or murmurs, but the apical first sound was roughened. No other findings of note were present. The size and configuration of the heart and great vessels were normal as determined by fluoroscopy.

Laboratory studies revealed normal findings, except that the original Kahn was reported positive. Two subsequent tests, without therapy, were negative, as was the Wassermann reaction. Erythrocyte sedimentation tests on three occasions were normal.

The electrocardiogram (figure 5–a) on admission resembled bundle branch block of the concordant type. It revealed a regular rate of 75 per minute, P–R interval of .11 second, slurred initial ventricular deflection, and minimum QRS duration of .12 second. RS–T segments were slightly depressed in Leads I and II, in which the T-waves were diphasic, with principal deflection downward. T_3 was inverted, while T_{4-F} was upright.

On December 11, after administration of atropine gr. 1/100 three times daily for three days (which produced symptoms of atropine effect) an electrocardiogram revealed a rate of 70 per minute, P–R interval of .08 to .10 second in different leads, and QRS duration of .10 to .14 second. The only significant alteration was seen in T_{4-F} which became dome shaped and of decreased amplitude. On the following day the contour of the positive T_{4-F} had returned to that of the original tracing. Two extrasystoles were noted (figure 5–d). One of them showed an even shorter P–R interval which measured .08 second, and a QRS, which, though similar to the usual complexes, was decidedly wider, measuring .15 second. This conforms to the description of auricular extrasystoles occurring in this syndrome, as reported by Wolferth and Wood.[5] The second extrasystole appears to be of ventricular origin.

Atropinization, using the same schedule, was repeated after an interval of one week. Examination after this period of medication (figure 5–b) revealed no alteration of P–R interval or of QRS duration, but it was found that T_1 and T_2 had become upright. T_3 showed little change, and T_{4-F} was of markedly decreased amplitude and altered contour.

Three days later the patient complained that he was having an "attack," and the pulse was found to be quite irregular with the rate recorded as 40 per minute. The apical rate approached 200 per minute but was also irregular. This irregularity was reflected in the sphygmomanometer, the blood pressure varying with each beat. The soldier was uncomfortable, but in no great distress, and walked into the ward office to report his condition. Carotid sinus and ocular pressure were ineffectual. Auricular fibrillation was suspected, but treatment, except sedatives, was withheld pending electrocardiographic study. The tachycardia persisted for four hours, and ceased

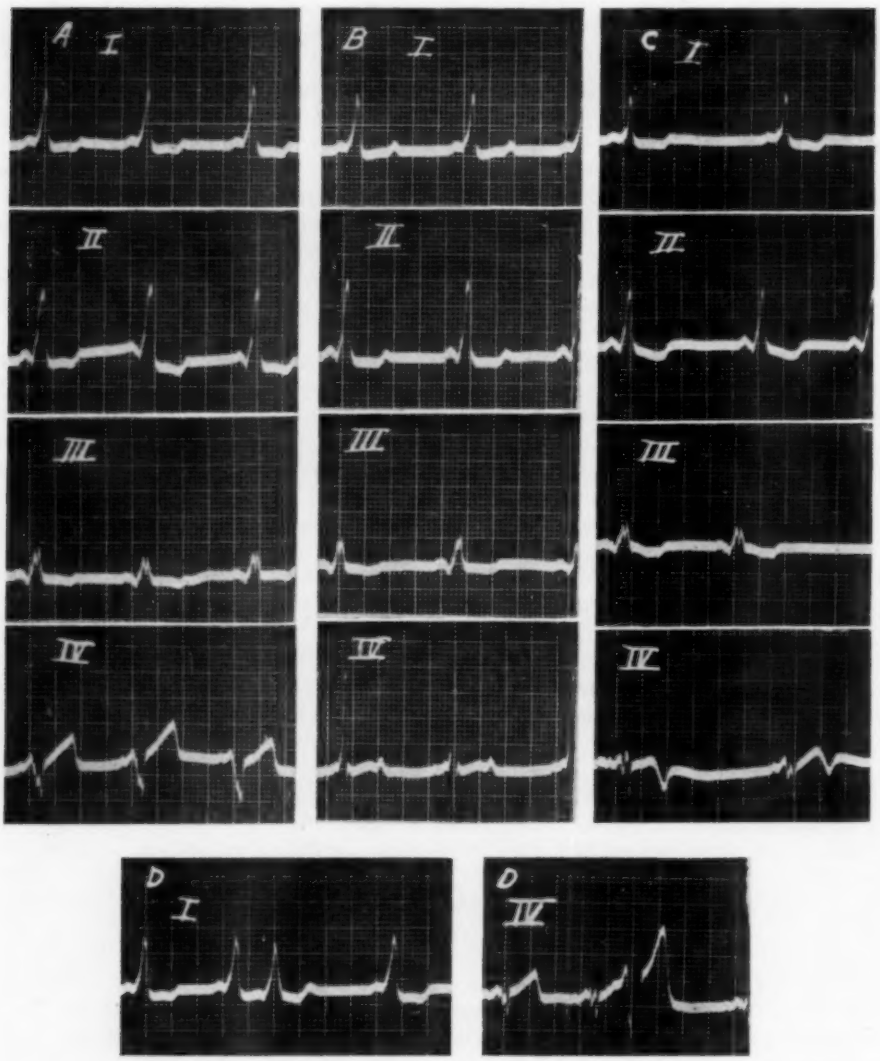

FIG. 5. *Case 4.* A—original; B—after atropine; C—after digitalis; D—supraventricular extrasystole in Lead I, ventricular extrasystole in Lead IV–F.

after spontaneous emesis. The electrocardiogram (figure 6–a) revealed that the attack had not been auricular fibrillation, but rather, ventricular tachycardia. On the following day the electrocardiogram (figure 6–b) revealed the Wolff-Parkinson-White pattern, but it was noted that T-waves were inverted in all leads, and QRS Lead IV–F was of an entirely different form. Several observers felt that the episode of the previous day had resulted from coronary occlusion, but there was nothing in the subsequent clinical course, febrile reaction, leukocyte count, or erythrocyte sedimentation rate to substantiate such a position. A tracing one month later (figure 6–c) revealed a pattern which was similar to that obtained on the day following tachycardia, except that T_{4-F} was upright.

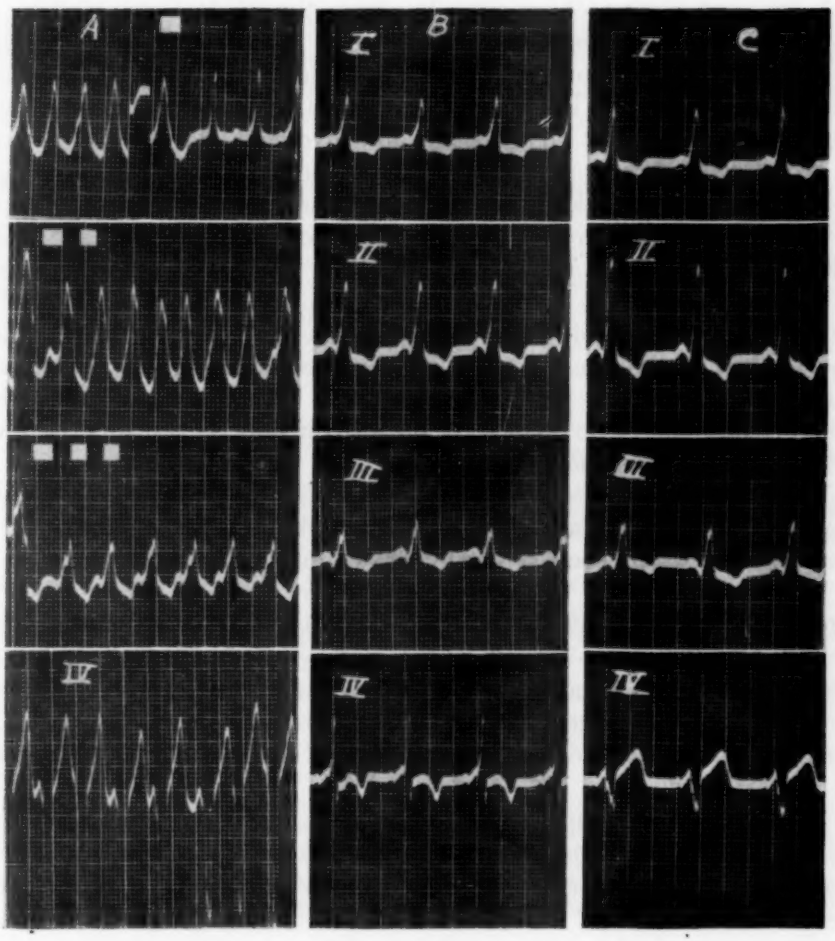

FIG. 6. *Case 4.* A—ventricular tachycardia; B—tracing obtained on following day; C—electrocardiogram after period of one month.

Following a control tracing several weeks later, which was identical with the original, the patient was fully digitalized, being given 27 grains of the drug in the form of powdered leaf tablets over a period of 26 hours. An electrocardiogram (figure 5–c) 15 hours after the last dose showed no significant changes in the limb leads except bradycardia and respiratory arrhythmia. In the fourth lead the ventricular complexes were of a distinctly different form, and the T-wave was diphasic rather than upright.

COMMENT

In addition to the common features previously enumerated these cases demonstrate all the variations so far described in association with the syndrome under discussion. Our fourth case showed a premature contraction which fulfills the criteria of a ventricular extrasystole. Such a complex has not been described in the several articles reviewed.

A most interesting observation has been the marked spontaneous and atropine induced variations in the T-wave. As for the former, case 1 presented at different times, without any medication whatever, T-waves of totally divergent form. These changes were not progressive, but varied from upright, through diphasic, to unquestionably inverted. Hartwell, White, et al. in a recent communication [6] report that, with normal subjects, a lowering of the T-waves in the limb leads is a rather constant finding following atropine. At variance with these results are the alterations in this group of patients with short P–R interval and prolonged QRS. In cases 1 and 4 the diphasic and inverted T-waves in Lead I were made upright. In view of the diagnostic import of marked T-wave changes, these results should be kept in mind. Therefore, to the imposing list, compiled by Sprague,[7] of factors influencing the terminal ventricular complex, atropine should be added. Similar changes may also occur spontaneously in subjects showing the Wolff-Parkinson-White syndrome.

The "paradoxical effect," previously mentioned, consisted of a totally unexpected bradycardia and respiratory arrhythmia after administration of atropine. This effect could not be duplicated in any of the other cases.

Wolferth and Wood [5] quote a case of Scherf and Schönbrunner wherein large doses of digitalis cause the temporary disappearance of the abnormal QRS complexes. Fox, Travell, and Molofsky,[8] on the other hand, report widening of the abnormal QRS complex with the same drug. Apart from the expected S–T changes, full digitalization in one of our cases (4) produced no appreciable effect. Neither the P–R interval nor the duration of QRS was altered.

We were fortunate in securing an electrocardiogram during the termination of an episode of paroxysmal tachycardia by ocular pressure. After asystole the ventricular complexes immediately assumed the Wolff-Parkinson-White form. Since this patient had also shown spontaneous reversion to normal sinus rhythm, we can only speculate as to the mechanism existing at the onset of tachycardia.

The onset of paroxysmal ventricular tachycardia in our last case, associated with marked apprehension, dyspnea, and precordial discomfort, was suggestive of an acute coronary episode, and, in fact, was held to be such by two observers. The possibility of such an error in diagnosis has been pointed out by Levine and Beeson [9] and should be emphasized. In this particular instance the clinical differentiation between paroxysmal ventricular tachycardia and auricular fibrillation was exceedingly difficult. The heart and pulse rates were totally irregular and were uninfluenced by carotid sinus or ocular pressure. There was a marked pulse deficit, and blood pressure was variable as would be expected with auricular fibrillation.

Summary

Four cases are reported, exhibiting the syndrome of short P–R interval associated with prolonged QRS complexes in patients with apparently un-

damaged hearts. Features in common with previously described cases are enumerated. All the variations ascribed to this syndrome are demonstrated, except reversion to normal rhythm after digitalis and quinidine.

Paradoxical atropine effects, a ventricular extrasystole, and recovery from auricular paroxysmal tachycardia are recorded.

Spontaneous and atropine induced T-wave changes are emphasized.

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I. TREATMENT OF EXPERIMENTALLY PRODUCED STAPHYLOCOCCAL THORACIC EMPYEMA*

By William E. Evans, Jr., Ph.D., James G. McAlpine, Ph.D., Benedict Skitarelic, M.D., and E. Howard Tonolla, M.D.,
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I. Introduction

The number of cases of thoracic empyema caused by the staphylococci is relatively small, but they present a difficult problem in therapeutics. The sulfonamide compounds have proved efficacious in the treatment of streptococcus infections but in those in which staphylococci play the major rôle, these drugs have not been, as a rule, beneficial. The present war with its multiplicity of gun-shot and shrapnel wounds will undoubtedly contribute its share of thoracic and abdominal empyema, and in a portion of these staphylococci will be present.

The production of staphylococcal empyema in experimental animals has not been very successful in the past although this would be the ideal method of study. After numerous failures a strain of staphylococcus was obtained which upon intrapleural inoculation would consistently cause thoracic empyema in rabbits without setting up a rapidly fatal septicemia. By this method it was possible to make detailed studies on the therapeutic effect of various preparations employing cultural and cytological technics with a terminal necropsy. This paper, which is the first of a series, embraces the study of a number of different combinations of drugs, and has as its objective the determination of those treatments which might be successful.

II. Historical

Inasmuch as Graham (1938), Ehler (1941), Carlson (1935–1936) and others have already reviewed the literature on empyema, it seems unnecessary to do so here.

The principles of treatment for thoracic empyema have been outlined by numerous clinicians, but those listed by Harrington (1931) cover the salient points. These are as follows: (1) adequate drainage, (2) avoidance of open pneumothorax, (3) rapid sterilization of the diseased area, (4) early obliteration of the cavity by expansion of the lung.

Menkin (1940), in his monograph on inflammation, has pointed out the sequence of the various phagocytic cells during the process of infection. He

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has also demonstrated the relationship of hydrogen-ion concentration to the cell picture in the infected area.

The origin and differentiation of the large mononuclear cells, or macrophages, which have been studied by Maximow (1932), Mallory (1914), Evans and Scott (1921), Sabin, Doan and Cunningham (1925), Cunningham, Sabin and Doan (1925), the Lewises (1925, 1926), Foot (1925), Permar (1924) and McJunkin (1919), are not within the scope of this article. It is concluded that all are phagocytic. The experimental studies of Gay and his collaborators (1921, 1926, a, b) on streptococcal empyema have shown the value of cytological examinations in infections of the thoracic cavity.

III. Experimental

Methods

1. Culture. The strains of *Staphylococcus aureus* which were obtained from human infections did not produce pathological conditions in rabbits. By the courtesy of Dr. J. Howard Brown of The Johns Hopkins University School of Medicine, a culture of the *G.V.S.* strain was obtained. This had been lyophilized since its original isolation in 1926 from a rabbit. In these experiments it was maintained on ordinary agar media without the addition of blood. An attempt was made to control the number of bacteria in order that a localized empyema might be obtained without the production of a fatal septicemia.

2. The Production of Empyema. A standard experimental procedure was adopted which was followed in all cases. A space was made in the right pleural cavity by the injection of 20 c.c. of air. Two days later the animal was inoculated with 0.3 to 0.5 c.c. (depending on the estimated number of organisms) of a 24-hour broth culture of *G.V.S.* staphylococcus. Two days after the inoculation, fluid was withdrawn from the pleural cavity. Then 10 c.c. of a solution of the therapeutic agent or agents were injected into and allowed to remain in the space. The treatment was repeated on the next two days. Pleural fluid was again withdrawn three days later. Smears and cultures were made after each aspiration. The animal was then killed with chloroform and the lungs were exposed by cephalad reflection of the pectoral girdle after lateral section of the ribs and transverse section at the level of the diaphragm. A culture of the heart blood was made. After observation of the condition of the pleural cavity, a portion of the right lung was removed for histological study. Specimens of liver and kidney were also removed for examination for possible damage resulting from the drugs used in the treatment. Rectal temperatures were taken in most cases before inoculation, two days after inoculation and on the day of autopsy. The determination of hemoglobin was made by the Sahli method in most cases at the beginning and end of the experiment to ascertain whether bacterial or

drug hemolysis was taking place. Since neither rectal temperature nor hemoglobin varied significantly, these observations were omitted in later experiments.

Materials

1. Animals. Rabbits weighing between two and three kilos were used.

2. Drugs. It was deemed desirable to restrict this study of the local treatment of empyema to a few drugs or agents, singly and in many combinations. Therefore, selections were made from classes of substances likely to be beneficial, i.e., immune serum, a chloramine antiseptic, a sulfonamide, and a wetting agent.

Azochloramid (1:3300) prepared from buffered tablets was chosen because it is relatively stable and non-irritating, and, as shown by Heise (1942) is active in vitro against the various staphylococcus toxins.

Sulfanilamide is the only sulfonamide which is appreciably soluble at a neutral hydrogen-ion concentration. An 0.8 per cent solution of this compound was employed.

A 0.2 per cent solution of sodium tetradecyl sulfate, properly neutralized, was used as a wetting agent principally because this compound has had clinical use in the treatment of empyema. The use of wetting agents locally is based on their ability to lower surface tension and thereby, theoretically, facilitate penetration of disinfectants. The literature on wetting agents has been reviewed by Frobisher (1929).

Solutions of these substances were prepared immediately before injection. When combinations of agents were used, solutions were prepared in such manner as to contain them in the foregoing concentrations.

3. Immune Sera. In order to produce an antibacterial serum for therapeutic purposes several groups of animals were injected intravenously with the living washed culture. It was thought that the living organisms were to be preferred for this purpose because there is no change in the antigenic structure. The rabbits were injected on two or three alternate days with varying amounts of the washed culture. Twenty-four hour broth cultures were centrifuged and brought to their original volumes with physiological salt solution. The usual dosages were 0.1 and 0.25 c.c. In two or three days the rabbits showed the effects of a generalized infection, i.e., emaciation and osteomyelitis. As a matter of expediency, that the animals might survive for bleeding purposes, intraperitoneal injections of one of the sulfonamides were given. In this way they were kept alive so that they might be bled on the twelfth and fourteenth days following the initial injections. Fatal bleedings were made from the heart, the serum separated, passed through a Seitz filter and preserved under aseptic conditions. The agglutination titer was 1–800. This immune serum was used in a 1:10 dilution.

Lederle's concentrated and refined antistaphylococcic serum in a dilution

TABLE I

Treatment	No. Rabbits		Pleural Fluid: Days after Treatment				Blood after 5 Days
			0	1	2	5	
Controls	8	Culture	+++			++++	+
		Smear	P_4 S D M_1 Ic_3 Ex_3			P_3 S D M_1 Ic_1 Ex_2	
A + SA	6	Culture	++++	++++	+++	++	< +
		Smear	P_3 S D M_1 Ic_2 Ex_2	P_4 S D M_1 Ic_3 Ex_2	P_1 D S $M_{occ.}$ Ic_2 Ex_1	P_2 D S M_2 Ic_2 Ex_2	
A + T	6	Culture	+++	+++	+++	+	+
		Smear	P_3 S D $M_{occ.}$ Ic_2 Ex_2	P_4 S D N Ic_3 Ex_2	P_3 S D $M_{occ.}$ Ic_2 Ex_2	P_3 S D $M_{occ.}$ Ic_2 Ex_2	
IS	6	Culture	++	+++	+++	++	< +
		Smear	P_1 D S $M_{occ.}$ Ic_1 Ex_2	P_2 D S M_2 Ic_2 Ex_2	P_2 D S M_2 Ic_2 Ex_2	P_3 S N M_2 Ic_2 Ex_2	
IS + FS	4	Culture	+++	+++	++	++	0
		Smear	P_1 D Ex_2	P_4 S D M_2 Ic_2 Ex_2	P_4 S N M_2 Ic_2 Ex_1	$P_{occ.}$ Bacteria rare	
IS + A	8	Culture	++++	+++	++	+	< +
		Smear	P_4 S D $M_{occ.}$ Ic_2 Ex_2	P_2 S Ic_2 Ex_2	P_3 S D $M_{occ.}$ Ic_2 Ex_2	P_1 S M_1 Ic_1 Ex_1	
IS + A + SA	8	Culture	+++	+++	+++	++	+
		Smear	P_2 S D M_2 Ic_2 Ex_2	P_2 S D M_2 Ic_2 Ex_1	P_2 D M_2 Ic_2 Ex_2	P_2 D M_2 Ic_2 Ex_2	
IS + A + SA + T	6	Culture	+++	+++	+++	< +	< +
		Smear	P_2 S D M_1 Ic_2 Ex_2	P_2 D S M_2 Ic_2 Ex_1	P_2 S D M_1 Ic_2 Ex_2	P_2 D S M_1 Ic_2 Ex_1	
T	4	Culture	++	+++	++	++	++
		Smear	P_3 N D $M_{occ.}$ Ic_1 Ex_1	P_2 N S Ic	P_1 N D Ic_2 Ex_2	P_1 N $M_{occ.}$ Ic Occ. Ex_2	

KEY TO TABLE I

A..... Azochloramid (1 : 3300)
SA..... Sulfanilamide (0.8%)
T..... Sodium Tetradecyl Sulfate (0.2%)
IS..... Immune Serum (1 : 10)
FS..... Fresh Serum (1 : 10)
P..... Polymorphonuclears
S..... Swollen
D..... Disintegrated
N..... Normal
M..... Macrophages
Ic..... Intracellular Bacteria
Ex..... Extracellular Bacteria
Occ..... Occasional
Subscript numbers refer to number on a 4 plus basis.

of 1 : 30 was used in other cases and did not appear to differ in effect from the serum prepared from the *G.V.S.* strain.*

4. Complement. Since it was found that the pleural exudates were very poor in complement, it was decided to add an equal amount of fresh serum

* This serum was supplied by the Lederle Laboratories.

to the antistaphylococcic serum. This was obtained by bleeding normal rabbits on the day before other animals were to be subjected to treatment.

Presentation of Data

The cultural and smear studies of the most promising methods of treatment are summarized in table 1.

Other methods of treatment employed were:

No. of Animals	Preparation
2	Azochloramid
2	Azochloramid, sulfanilamide, and sodium tetradecyl sulfate
2	Azochloramid, sodium tetradecyl sulfate, and immune serum
2	Normal serum
2	Normal serum and azochloramid
3	Normal serum, azochloramid, and sulfanilamide
6	Sodium tetradecyl sulfate, and immune serum
2	Sulfanilamide
2	Sulfanilamide and immune serum
2	Sulfanilamide and sodium tetradecyl sulfate

Gross Study. Necropsies were performed on all the animals at the end of seven days. On the treated side all showed atelectasis and a white thick shaggy exudate in varying amounts. Those treated with sodium tetradecyl sulfate contained particularly large amounts of fibrin. Adhesions were present in varying degrees between the visceral and parietal pleurae. There was a serous blood tinged pleural effusion on the contralateral side in three of the animals.

Sections of the lungs, the kidneys, and the liver were removed for microscopic study.

Microscopic Study. The kidneys and livers showed no significant lesions. The lungs in general were atelectatic in varying degrees in all cases, the compression usually being in direct proportion to the amount of exudate present. The pleurae were slightly thickened and displayed many small dilated capillaries. Some subpleural pneumonitis was present in all cases, as evidenced by polymorphonuclear infiltration deep in the interstitial tissue. Most of the lungs were moderately congested. The alveoli and the bronchi remained clear; there was no evidence of a pneumonic process except for the above mentioned subpleural involvement.

The pleural exudate of all the controls was loaded with polymorphonuclears, and there were many small areas of abscess formation present. No fibrin was seen. Atelectasis was almost complete.

The animals treated with azochloramid and sulfanilamide showed moderate amounts of fibrinous exudates which contained mainly polymorphonuclear leukocytes. These cells also invaded the interstitial lung tissue in varying numbers. Few mononuclear phagocytes were seen.

The animals treated with azochloramid and sodium tetradecyl sulfate showed varying amounts of fibrin in which were seen only small scattered

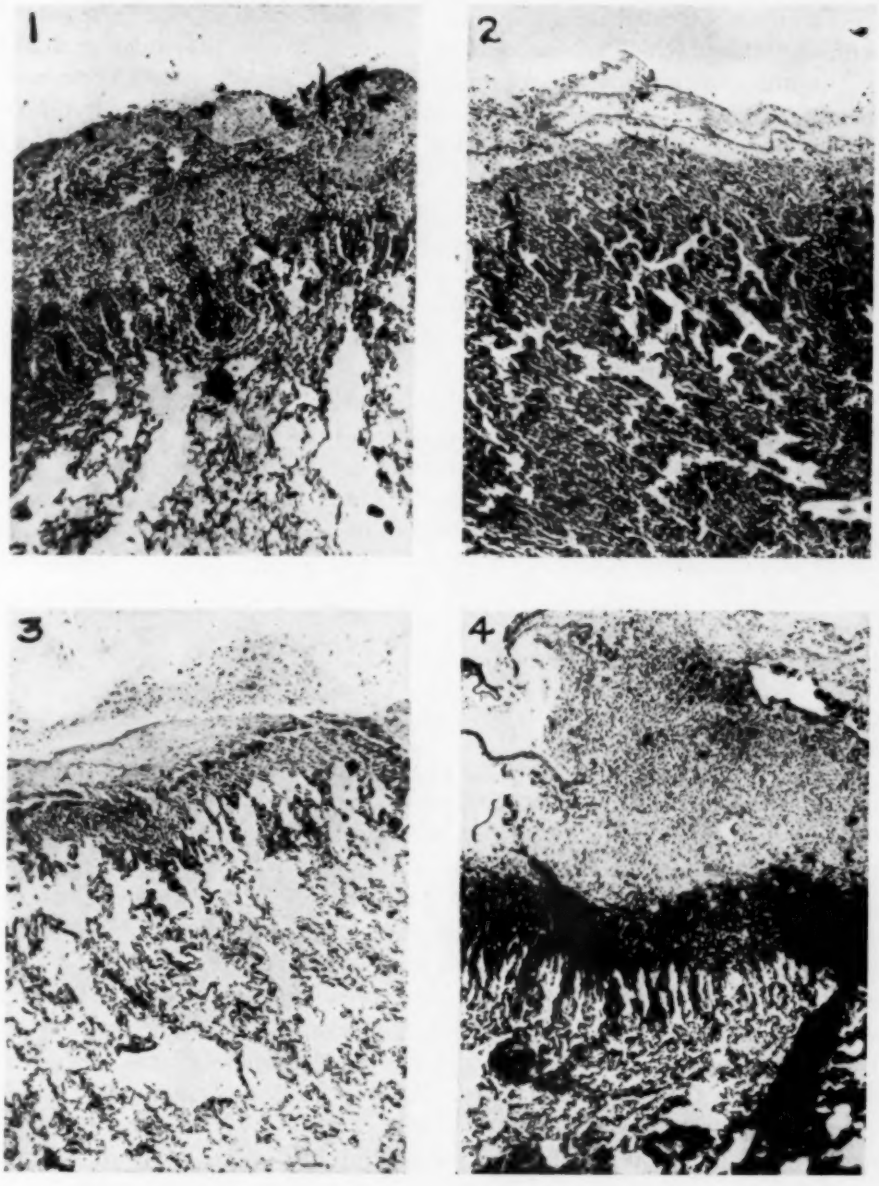

FIG. 1.

1. Control
2. Azochloramid and sodium tetradecyl sulfate
3. Sodium tetradecyl sulfate
4. Immune serum

wandering cells, most of which were polymorphonuclears. There was a slight fibroblastic proliferation on the visceral pleura. The lung parenchyma showed no change.

The animals treated with immune serum revealed a moderate amount of fibrinous exudate which was moderately infiltrated with polymorphonuclears.

The animals treated with immune serum and fresh serum contained a moderate amount of exudate in which the mononuclear phagocytes predominated. Much of the exudate was acellular. Only an occasional polymorphonuclear was seen.

The animals treated with immune serum and azochloramid showed small amounts of fibrin; the polymorphonuclear and monocytic forms were about equally distributed.

The animals treated with immune serum, sulfanilamide, and azochloramid contained only a scant amount of fibrin in the exudate. Most of the cells were disintegrated.

The animals treated with immune serum, azochloramid, sulfanilamide, and sodium tetradecyl sulfate showed little pleural exudate which contained a few polymorphonuclear and mononuclear phagocytes in its meshes. For the most part the lungs were completely collapsed and the pleura was covered with a scant amount of fibrin. There was an increased amount of subpleural pneumonitis present.

The animals treated with sodium tetradecyl sulfate showed a moderate amount of fibrin and a fibroblastic proliferation of the pleura. The mononuclear phagocytes were predominant.

IV. Discussion

The short treatment period was decided upon in order to eliminate the greater number of the possible therapeutic agents and combinations of agents from further consideration. An exhaustive study of the remainder would then be practical. It was realized that complete sterilization of the cavity could not be attained within such a short period. Selections were based on culture studies, smears of the pleural exudates, gross findings on autopsy, and histological studies of the lung and pleura on the treated side.

The cultures obtained from the untreated animals showed an increase in bacterial content during the experimental period. In all the other selected groups there was a diminution in the estimated number of microörganisms to 1–2 plus on the day of necropsy. Blood cultures with the exception of those animals treated with sodium tetradecyl sulfate were never over 1 plus. Inasmuch as the amount of fluid which could be aspirated from some animals was relatively small, direct bacterial counts were not attempted. The standard procedure was to place three drops of the aspirated fluid on an agar slant and incubate for 48 hours. The number of bacteria which had appeared at that time was recorded on the 4 plus basis. For the blood cultures the same technic was adopted.

Smears on the first day before treatment, i.e., 48 hours after infection, showed large numbers of polymorphonuclear leukocytes, mostly swollen, some disintegrated, and occasional macrophages. At this stage of the

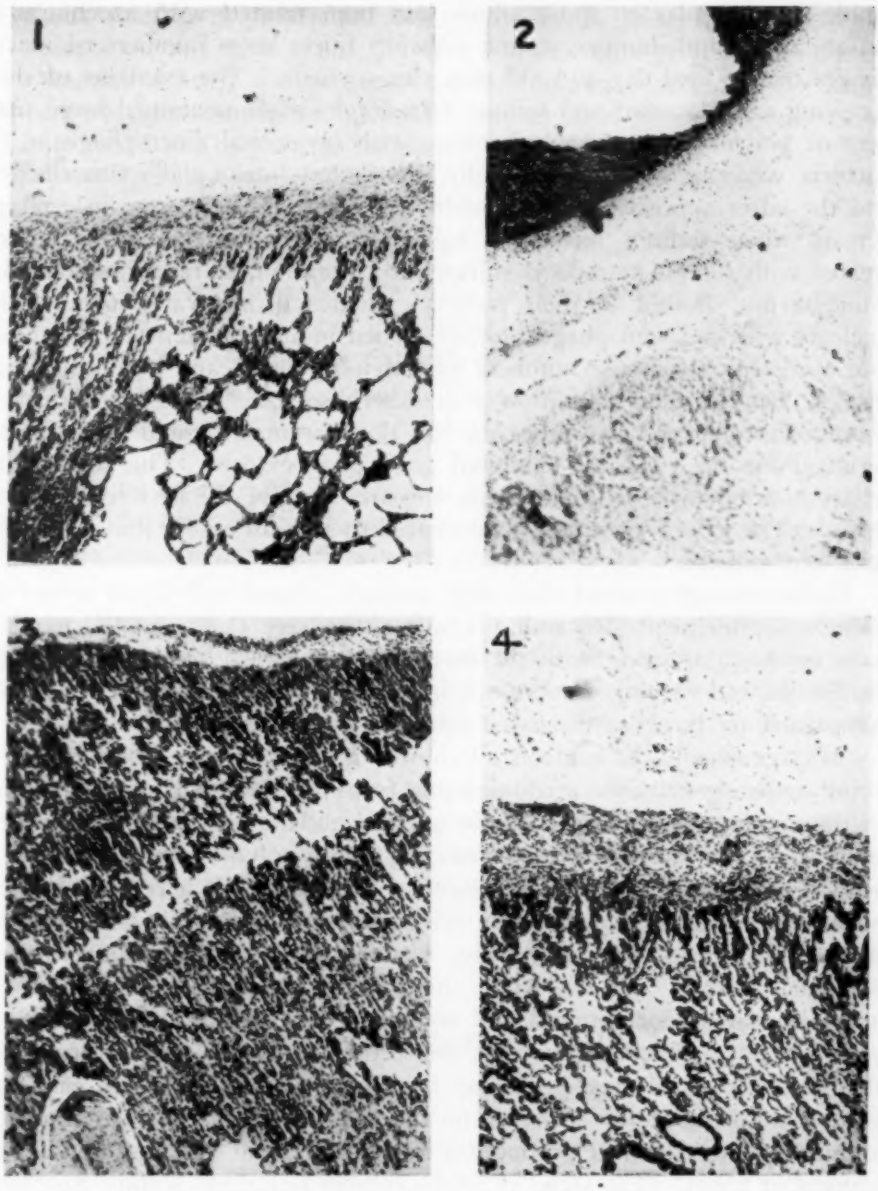

FIG. 2.

1. Immune serum, azochloramid, sulfanilamide and sodium tetradecyl sulfate
2. Azochloramid and sulfanilamide
3. Immune serum and azochloramid
4. Immune serum and fresh serum

infection phagocytosis was relatively good. In the controls on the final day the phagocytosis was less and the bacteria more numerous extracellularly. The pleural smears of the animals treated with azochloramid and sulfanil-

amide were similar to those which had been treated with azochloramid, sulfanilamide and immune serum, showing fairly large numbers of macrophages on the final day and a 3 plus phagocytosis. The exudates of those receiving azochloramid and sodium tetradecyl sulfate contained large numbers of polymorphonuclear leukocytes, with occasional macrophages. The bacteria were approximately equally distributed intra- and extracellularly, and the latter appeared to be enmeshed in fibrin. There was little phagocytosis when sodium tetradecyl sulfate was used alone. The animals treated with sodium tetradecyl sulfate, azochloramid, sulfanilamide and immune serum showed in their pleural exudates disintegrated polymorphonuclears with excellent phagocytosis. When immune serum and azochloramid were employed, the numbers of polymorphonuclears were small, and though swollen their condition was otherwise excellent. The infectious process showed favorable progress. In those animals treated with immune serum alone the exudates exhibited good phagocytosis. The combination of fresh serum with immune serum appeared to give the best results in the series. The infectious process had cleared to such an extent that only a few cells were present.

Gross findings showed that those animals treated with fresh serum and immune serum responded well. The cavities were clear and the exudates were minimal, agreeing with the foregoing cytological and cultural results. Others showed varying amounts of infection and exudates which were also comparable to the above discussed results.

Microscopically the controls all showed a great amount of exudate, rich in inflammatory cells, the predominating form being the polymorphonuclears. In those treated with azochloramid and sulfanilamide there were moderate amounts of fibrinous exudate containing many polymorphonuclears. This process was still active after five days of treatment. Where azochloramid, sulfanilamide and immune serum were employed the sections showed the presence of thick fibrin and many disintegrating polymorphonuclear and mononuclear cells. On the whole this process appeared favorable. In the series in which azochloramid and sodium tetradecyl sulfate were used no great amount of fibrin appeared in the sections, although it was very noticeable in the gross findings. It may have been stripped off with ease since fibroblastic proliferation was seen on the pleura. In the inoculated animals sodium tetradecyl sulfate produced a moderate cellular response and an outpouring of fibrin. The series in which sodium tetradecyl sulfate, azochloramid, sulfanilamide and immune serum were employed showed very little exudate, and there were only a few inflammatory cells present in its meshes. A favorable result was evidenced in this series. In animals treated with immune serum and azochloramid, the sections showed a small amount of fibrin and the polymorphonuclear and mononuclear forms were about equally distributed; only one animal exhibited a residual infection as shown by the presence of a relatively few inflammatory cells. Where immune serum

alone was used the polymorphonuclear response was great, fibrin was scant, and several animals were practically free from exudates. In sections from those animals treated with fresh serum and immune serum, the exudate was scant and practically acellular with mononuclear forms predominating and only occasional polymorphonuclears.

Representative photomicrographs of each series are appended.

V. Summary and Conclusions

This problem was limited to the study of pleuritis produced by a special strain of *Staphylococcus aureus*. No other organisms have been used.

The following possibilities are suggested:

1. Immune serum alone appeared to stimulate an earlier and greater response on the part of the mononuclears and the animals were obviously benefited.

2. Immune serum with complement also produced an early and active response on the part of the mononuclears. Phagocytosis was more marked, and by the seventh day bacteria were either markedly reduced or absent. Little exudate remained.

3. In other cases in which azochloramid was used in combination with other agents the results in general were: increased phagocytosis in some cases, and increased exudate of serum and fibrin in other cases. The fibrin in the latter showed favorable lysis and the fibroblastic proliferation in the pleura was scant.

4. The reactions in the animals treated with sulfanilamide, sodium tetradecyl sulfate, and azochloramid, were more favorable than in the controls, but less favorable than in the immune serum-complement series.

5. Those methods of treatment which appear to merit further study are: (1) azochloramid and sulfanilamide, (2) azochloramid and sodium tetradecyl sulfate, (3) immune serum and fresh serum, (4) immune serum and azochloramid.

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SPONTANEOUS COMPLETE RUPTURE OF THE AORTA WITHOUT DISSECTING ANEURYSM, WITH REPORT OF A CASE SHOWING A NEW PHYSICAL SIGN (PERIAORTIC FRICTION RUB) *

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Introduction

Rupture of the aorta is by no means rare. Until comparatively recently, the commonest cause was probably a syphilitic aneurysm. With modern methods in the treatment of syphilis, however, such aneurysms have become much less common than formerly.

The causes of complete rupture of the aorta may be classified as follows:

1. Major trauma. This may be a direct piercing injury, as from a bayonet, bullet, etc.; or a severe, non-penetrating, crushing injury to the chest, such as occurs when a person is injured by a "cave-in" or falls from a high place.

2. Minor trauma combined with one of the factors listed below. When the aorta is "ripe" for "spontaneous" rupture, a relatively light blow on the chest or back, a fall from a horse, or a sudden strain, caused by lifting a heavy object or straining at stool, may precipitate the rupture. Several cases of aortic rupture during labor have been reported, especially in the German literature.[5]

3. Syphilis of the aorta, usually aneurysm, occasionally a simple syphilitic aortitis.

4. Atherosclerosis of the aorta with gross necrotic areas in the wall.

5. Mycotic aneurysms.

6. Extrinsic disease, such as tuberculosis, malignancy, septic processes, etc., damaging the aortic wall by extension, with or without thrombosis.

7. Coarctation, often associated with mycotic aneurysms.

8. Congenital hypoplasia of the aorta.

9. A condition in which the aortic wall is of paper-like thinness.

10. Dissecting aneurysm independent of any of the above factors (except minor trauma, which may be present or absent).

11. A condition where no gross change can be observed in the aortic wall.

In the cases associated with major trauma, syphilitic aneurysm and congenitally thin aortic wall, the mechanism of rupture is obvious. In all the

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other types of rupture, except those due to syphilitic aortitis and those in which there is no gross change in the vessel wall, it is usual for a dissecting aneurysm to be formed before complete rupture occurs. Hypertension is often an important additional factor, and is practically always present in cases of coarctation above the stricture, where the rupture occurs.

Even excluding major trauma and syphilitic aneurysm, the literature on spontaneous rupture of the aorta, usually with associated dissecting aneurysm, is quite voluminous, far more so than the files of clinical and pathological journals would suggest. Although a considerable number of articles on the subject may be found in such journals, it is in the anatomical literature, especially in that of France, that one finds the greatest wealth of material. One publication, *Bulletin et Mémoires de la Société Anatomique de Paris,* going back for over a century, lists more than 50 articles on spontaneous rupture of the aorta, usually with dissecting aneurysm. One of us collected a bibliography of some 300 articles on the subject, about one-third of which he was able to verify personally. As the subject of this paper excludes dissecting aneurysm, it seems unwise to occupy space with such an extensive list of references, most of which have no special bearing on our subject. All the articles which could be verified on spontaneous rupture without gross defects in the vessel wall at the point of rupture will, however, be listed, as well as a few others having some special bearing on this paper.

Some Previous Clinical Observations. According to Bright,[6] Vesalius suspected that ruptures of non-aneurysmal aortas occur and predicated them without any clinical evidence.

Morgagni [30] reported several cases of rupture of the aorta in his famous work on the seats and causes of disease, first published in 1761. Some of these were associated with ordinary aneurysms, some with dissecting aneurysms; but in two cases no obvious disease of the aorta is mentioned, though minor trauma occurred in one of them. In Letter XXVI he treats "of sudden Death, from a Disorder of the sanguiniferous vessels, especially those that lie in the Thorax." In that letter we find the following:

"6. But the great artery is sometimes eroded, even without an aneurysm, and pours out its blood, as the next very short history teaches.

"7. A certain man was taken off by a sudden death, in the latter end of June, in the year 1689. Permission being obtained, with great difficulty, from the relations to dissect the body, the aorta was found to be ruptured where it was nearest to the heart; and the pericardium was from thence quite full of coagulated blood."

In Letter LIII, Art. 35, we read:

"An old man, being busy in cutting wood in the forest of another person, was caught by the master of the forest in the middle of his theft. The master first blamed him, which was answered from the old man by curses and threats; and at length, as the old man was running away, the master struck him on the back, only once, with a club. The man fell down dead from the blow, after going two or three paces.

"The great artery was found to be ruptured transversely, and cleft asunder; notwithstanding the vertebrae and ribs were sound and unhurt."

The next description of a case of rupture of the aorta without mention of any evidence of dissecting or other aneurysm which we have been able to find in the

literature is that of Rose [37] in 1828. This was the case of a 65 year old man, tall and strong, who had had chronic rheumatic pains, but whose health seemed otherwise good. Fifteen days after his general good health had been established by an examination, he got into a violent argument and felt a sudden intense pain beginning in his chin and radiating along the great vessels of his neck, down into his chest and back. It was so severe that he had to lie down in the field. The pain lasted through the night and into the next day, when Rose saw him. At this time he was lying supine, his arms stretched out at his sides, avoiding the slightest movement. His pulse varied from 96 to 100 per minute. His tongue was moist, with a brownish tint to its central part; his face showed suffering; his respiration was easy, but the pain, especially in his back, increased, and from time to time went through his chest. The day after this his pain was much less, and he enjoyed bouillon. At 8 p.m., however, he displayed great agitation and "obstinate tenesmus" (whether vesical or rectal, the account does not state). At 9 p.m. his pain was worse, he changed his position constantly, his pulse was weak and irregular, he had a generalized cold sweat and seemed moribund. He responded to stimulation, but at 4 o'clock the next morning, on trying to get up and go to the toilet, he suddenly died. In the arch of the aorta, on the concave side, was a slit, the edges of which showed no sign of ulceration. There was an enormous clot in the posterior mediastinum and between the lungs and pleurae, with marked infiltration into the thoracic intercellular tissue.

A third case of interest is that of DeAngelis [2] in 1836, for it is the first report known to us in which the patient was stated to be a relatively young person. Here, in a 35 year old man, moderate trauma may or may not have been a factor, for he fell from a ladder "about the height of a man." About an hour later, after eating as usual, he remarked on getting up from the table that the fall had not hurt him. He got back on the ladder and resumed his work of picking olives. In the evening he went home, carrying the ladder on his back. On getting home, he felt sick and had to go to stool. After defecating, he fell dead. An enormous amount of blood was found in his left pleural cavity. This had separated into clot and serum, the total amount weighing about seven pounds. There was a tear in the descending aorta at the level of the seventh rib. The pericardium, heart and lungs were healthy.

Sibley's case,[39] reported in 1864, is of some special interest because of the extraordinary pathological findings. The absence of a dissecting aneurysm in the ruptured aorta, and the presence of one elsewhere, make the case unique. The patient was a messenger aged 53, of small stature, stout and florid. His previous history was negative save for occasional "bilious attacks." He went one evening to wait on a dinner table. In the kitchen he complained of gaseous distention with inability to get up the gas, and asked for some brandy and potash water. He was speaking cheerfully and was turning to go out of the kitchen, when he fell down, gave one or two gasps, and died. At necropsy the pericardium was found to be distended with dark fluid and contained a pound of coagula with about an equal amount of liquid. The pericardium itself was healthy save for a slit where it was reflected over the great vessels. The heart was rather large and pale. The valves were healthy except for slight traces of atheroma. The aorta was considerably dilated, and a large transverse rent was found, involving fully two-thirds of the circumference of the aorta, about an inch above the aortic valves. The rupture extended through the whole substance of the vessel, which showed no dissecting aneurysm. There was some atheroma, but it was neither extensive nor advanced. There was, however, a dissecting aneurysm in the subclavian artery, but this apparently had nothing to do with the rupture of the aorta.

In Browning's case [8] of a 34 year old blacksmith, reported in 1871, in which rupture occurred into the pericardium with instant death, the rupture "was attributed

to the giving way of a small atheromatous spot," but whether this was an observation or an assumption is not clear.

In 1892 Brouardel and Vibert [7] reported a unique case of rupture due to a remarkable condition which could not be detected clinically. As we know of no other such case on record, it is summarized for its historical value, and also to illustrate the ninth heading in our classification of causes of ruptured aorta. The patient was a 20 year old medical student. He had had some minor convulsions in the first year of his life, and a very severe case of typhoid fever at the age of five years, when he "hung between life and death for three months." He had no illness thereafter until his final one, and had been active, worked hard, run with his comrades, and had had no dyspnea, palpitation, syncope or hemorrhages. After a day's work in the dissecting room he went home about 8 p.m., wrote a gay letter to a friend and went to bed. That night he felt abdominal pain and said he had colic. He went to the toilet at 4 a.m., but had no diarrhea. His pains persisted and localized in the liver region. Dr. Collardeau saw him at 8 a.m., thought of the possibility of "hepatic colic," and prescribed a purge followed by laudanum, and a potion. About noon Dr. Collardeau found the patient's pains worse and the bilious vomiting persisting. At 6 p.m. the pain was much worse, forcing the patient to cry out. At 7 p.m. he asked for some lemonade, then suddenly sat on his bed, cried out twice, seized his mother's arm, squeezed it hard for only a moment, and then fell dead. At necropsy the right pleural cavity was found to contain 250 grams of uncoagulated blood. There was also a large pocket containing 1800 grams of liquid and coagulated blood which communicated with the posterior mediastinum, the cellular tissue of which was infiltrated with coagulated blood. The lungs were normal. The pericardial cavity contained two coffee cupfuls of reddish liquid. The blood around the aorta extended up to the retropharyngeal cellular tissue, and down to the iliac arteries, on the left side even going "through the crural ring to the emergence of the deep femoral." The aorta showed two transverse ruptures: "one 2½ cm. long, 3 cm. below the beginning of the left carotid; the other 25 mm. long, 3 cm. below the diaphragm." The aortic diameter was small; opened and spread out, the aorta was 42 mm. wide. It was of a paper-like thinness. Under a magnifying glass, little tears became visible in addition to the larger ones. All the other arteries examined, including the left carotid, left femoral and basilar, seemed normal. Histologically, there was complete degeneration of the media. Brouardel and Vibert believed the condition of the aorta to be due either to the severe typhoid fever at the age of five years, or to a congenital anomaly.

Until the opening of the present century, the interest in our subject had been largely anatomical. Since then, however, increasing clinical interest has been taken in spontaneous aortic rupture, and important contributions have been made to our knowledge of the pathology of the condition. In the early part of the present century, very extensive clinical studies were made by Bright,[6] by Gardette,[17] and by Achard and Paisseau.[1] More recently, Hamman [21] has made a brilliant contribution, making an antemortem diagnosis of rupture of the aorta (with or without dissecting aneurysm) from the record of a patient. The most notable contributions to the pathology of the condition appeared in Germany in 1929 and 1931, by Erdheim [14] and Cellina,[9] respectively. In 1932, Moritz [31] gave an able discussion of the subject in the United States. Rochard and Debelly [36] reported a remarkable case occurring at the beginning of a laparotomy, in which the abdominal aorta ruptured, the rupture was sutured, and the patient survived for three

and one-half hours. The blood was found escaping into the peritoneal cavity when the abdomen was first opened.

Kaufmann's patient,[23] a groom aged 19, was admitted to Queen's Hospital, Birmingham, England, almost unconscious. The next day, however, he was able to give his history. For a month previous he had complained of an aching, sometimes shooting pain in the back of his lower chest about the level of the eighth thoracic vertebra, worse on exertion, but not on deep inspiration. He had no cough. Thirteen days before admission a doctor gave him a bottle of medicine without examining him; his pain was relieved and did not trouble him again for 10 days. On its recurrence, the treatment was repeated, this time without benefit. He kept working for the next three days, but then, about 2:30 p.m., soon after dinner, his pain became very much worse. He stopped work and caught an omnibus a few yards away without running for it, and started home. Within five minutes the guard noticed that he looked very ill. He called a physician, who found him collapsed and pulseless, gave him strychnine, and sent him to the hospital. There was no history of chest injury, no cough or indigestion, and no evidence of tuberculosis or syphilis. On admission he was pale, slightly cyanotic, partly conscious, restless and in great pain. His pulse was rapid and very small. His abdomen was rigid, but not distended, and there was no dullness in the flanks. There was considerable tenderness in the right hypochondrium. No abnormal masses were felt. The sternum was prominent, and the left side of the chest hardly moved in respiration. A palpable "apex beat" was noted in the third interspace in the *right* nipple line. The left axilla was dull up to the fifth rib, and above this a low-pitched tympanitic note was obtained, reaching as far to the right as the midline and upwards almost to the clavicle. Behind, the left chest was dull up to the seventh rib, and above this the dullness shaded off to a normal note at the apex. Over the very dull area no breath sounds could be heard, and vocal fremitus was absent. In the hyperresonant area, faint breathing with prolonged expiration was heard, and in the partly dull area, diminished, though rather harsh, vesicular breathing. There was no change in the percussion note over the right lung, and the breath sounds, though harsh, were vesicular. The "anvil sound" (coin sound) was heard well over the third and fourth left interspaces in front. There were no heart murmurs. The temperature was 98.2° F., pulse rate 120, and respiratory rate 28. The day after admission he was still very pale, but fully conscious and less restless. His abdomen was rigid and retracted slightly on inspiration, the recti hardening on expiration. It was tympanitic throughout. At a second examination there was slight tenderness in the left hypochondrium, none elsewhere. The physical signs in the chest were unchanged except that the hyperresonant area extended to the right of the sternum and was of higher pitch than before. As the patient was evidently suffering greatly from increased pressure in the left chest, thoracentesis was done in the fifth interspace in the left anterior axillary line at about the upper limit of dullness. A mercury manometer showed a positive pressure of 35 mm. with expiration. About 2 ounces (60 c.c.) of air and 10 to 12 drams (40 to 48 c.c.) of dark fluid blood were then withdrawn. The intrathoracic pressure fell considerably, but blockage of the cannula and tubes with clots made further measurements unreliable. Just after tapping, the hyperresonant note was much less high-pitched and did not reach quite to the right edge of the sternum.

On the third day after admission, the patient's temperature was 99.6° F., but his general condition was much better. For the first time, a soft systolic whiff was heard at the first left cartilage, and a similar one immediately after the first sound in the third right interspace at the point of maximum pulsation. The rigidity and tenderness of the abdomen had almost entirely disappeared; there was more dullness in the left chest (the whole axilla being dull), but expansion was increasing. Two

days after this the patient was much better, and the chest tympany did not transgress the midline. The upper left chest, as far down as the third rib, gave a loud tympanitic note, thence to the fifth rib a shallow "tubular" note, and below that, absolute dullness. The heart remained as before, but a slight epigastric pulsation, probably representing the true apex beat, was now felt. After another two days, at 9:20 a.m., while apparently doing well, the patient cried out suddenly with pain in his left chest and became blanched and covered with cold sweat. He was given morphine, but died in 20 minutes. During this time the dullness in his left side rose much higher. He had no vomiting in the hospital, and only an occasional short dry cough. The urine only once showed a trace of albumin (the day after admission) and no casts or blood were found in it.

At necropsy, the heart was found to be completely in the right side of the chest, and a large blood clot was found between the front of the left lung and the chest wall, coming from an oblique tear across the descending aorta which must have existed some days, as it showed signs of inflammation and some repair. The aortic wall appeared healthy, but rather thinner than usual.

Some features of special interest occurred in the case of a 44 year old man reported by Achard and Paisseau.[1] While at dinner with his family he was taken violently ill with great dyspnea and was sent to the hospital. On his arrival, his dyspnea had moderated somewhat, but he complained of deep "localized" thoracic pain, and remarked that he felt as if a blood clot were forming in his throat! He had no hemoptysis, was restless and thirsty during the night, and got up several times to drink great quantities of water. In the morning, being unable to rest in bed because of increasing dyspnea, he sat up in a chair. In about half an hour he complained of violent pain, got up suddenly, fell unconscious and died within a few seconds after being carried to his bed. This patient had been an acrobat and weight lifter and had "copiously fêted Venus and Bacchus." His rupture being associated with a dissecting aneurysm, falls outside our group; but the feeling of a clot forming in his throat was so striking that it seems worthy of mention here.

Other contributions from various standpoints are noted in the bibliography.[3, 10, 11, 13, 20, 22, 26, 27, 28, 29, 32, 33, 35, 42]

Authors' Case Report

The patient was a 48 year old farmer who, because of a crippled knee, found it difficult to do heavy winter farm work such as logging, and therefore operated a planer in a furniture factory in the winter months. One of us had examined him some 15 months previously, at which time the diagnosis was hypertensive cardiovascular disease, arteriosclerosis, a mild left hemiplegia due to a cerebral vascular accident, which seemed to be improving, and dental sepsis due to pyorrhea, crowned teeth, etc. His blood pressure at that time was 240 mm. Hg systolic and 120 mm. diastolic. His condition steadily improved after dental treatment, so that by January 25, 1941, his blood pressure was 210 mm. Hg systolic and 110 mm. diastolic, he could use his left side quite satisfactorily, and was working regularly.

On January 29, 1942, just as he started to eat lunch in the furniture factory, he had a slight pain under the xiphoid. He consulted a physician who thought he had indigestion and gave him a purgative, though his bowels were quite regular and had moved that morning. He returned to work in the factory. About 4 p.m. he was seized with a very different, agonizing pain, also under the xiphoid. The same physician whom he had seen at lunch time was called, and feared that the patient had had a gastric hemorrhage, though there had been no nausea or vomiting. He advised immediate admission to a hospital. The patient was sent in an ambulance to the

Burrus Memorial Hospital in High Point. On arrival he showed an ashy cyanosis and was obviously suffering extreme pain in the xiphoid region. His pulse was very tense. About 6 p.m. his blood pressure was 212 mm. Hg systolic and 130 mm. diastolic. At 7 p.m. it was 220 mm. Hg systolic and 146 mm. diastolic. At this time his white cell count was 20,400, with 96 per cent neutrophiles. Physical examination showed practically nothing except the facies of extreme pain and near-collapse, profuse sweating and visible and palpable sclerotic superficial vessels. His lungs were clear at this time in front, and apparently clear in the back so far as could be ascertained from slipping the diaphragm of a stethoscope under his back. He seemed too ill to justify turning him over or raising him in bed. A surgeon examined him and agreed that no condition requiring operation was present.

At 11:45 p.m. he was sleeping after a second dose of 1/4 grain of morphine and 1/150 grain of atropine. His pulse showed a rate of 88 and was less tense than on admission. A fall in blood pressure was suspected but rest was so imperative that he was not disturbed to take his pressure. His abdomen was soft. Another surgeon looked at him and agreed that he did not have any surgical abdominal condition. The next morning the patient's systolic pressure had dropped 90 mm. Hg. Further examination was postponed because of his need of rest. However, he looked very ill, so that afternoon a cardiologic consultant was called. In addition to the findings already described he noted the following points: The pain was decidedly worse with respiration and was much relieved by holding his breath; there was a definite paradoxical pulse with the inspiratory pressure 15 mm. below the expiratory; the expansion of the left chest was diminished, especially in the upper part and there was prominence of the left chest, especially in its upper portion; there was obliteration of cardiac dullness on the left, because of striking drum-like tympany over the left upper lobe anteriorly, with dullness to the right of the sternum and evident displacement of the heart to the right; there was obliteration of the point of maximum impulse, with systolic pulsation of the entire left chest; flatness and marked dullness were noted to the right of the sternum and tubular breathing in the left base and axilla. A to and fro friction rub synchronous with the heart beat was heard in the suprasternal notch and faintly along the right and left sternal margins. There was also a poorly audible "klunk" heard best in the suprasternal notch and but faintly over the base of the heart.*

Hemopneumothorax was suspected and coronary occlusion excluded. At this point it was decided to attempt to make some roentgen-ray films of the patient's chest. Now another interesting symptom appeared, viz., that the patient would apparently start to suffocate and have agonizing pain if he turned on his right side, as if something were cutting off his airway, so he was not allowed to do this further.

The roentgenologic report, by Dr. P. W. Flagge, was as follows:

"(1/30/42) Flat anteroposterior and posteroanterior in lateral position. The flat anteroposterior position shows the left side of the chest generally clouded, with the mediastinum pushed far to the right, apparently ¾ inch beyond the right border of the heart. This line runs almost straight up and down the chest on the right side, about 2½ inches beyond the right margin of the spine. The left lung is generally clouded, though it appears collapsed. The free cavity is filled with some opaque fluid which leaves the impression of the shadow of blood, because of the irregularity of the density. The diaphragm is pushed far down. The 'lat.' (posteroanterior with patient lying on left side) film shows nothing except a cloud on the left side with the mediastinum shifted back toward the left side, close to the margin of the spine. The right lung appears to be normal."

* This hitherto undescribed aortic friction rub was discovered by the cardiologic consultant, Dr. Tinsley R. Harrison, and we suggest that it be known in the future as "Harrison's sign." The "klunk" presumably was the sign described by Skerrett.[40]

At two o'clock the following morning, the patient's nurse reported that he had coughed, and was immediately seized with an agonizing pain along the course of the left clavicle. A competent nurse of long experience, she described it as about the worst pain she had ever seen a patient have. Then his pupils dilated and he appeared to be dying. Additional morphine was ordered. Soon he revived somewhat and was suffering less. A few minutes later he made an effort to sit up, as if to breathe better, and again developed extreme pain along the left clavicle and struggled hard to get his breath. He then turned on his left side and became more comfortable.

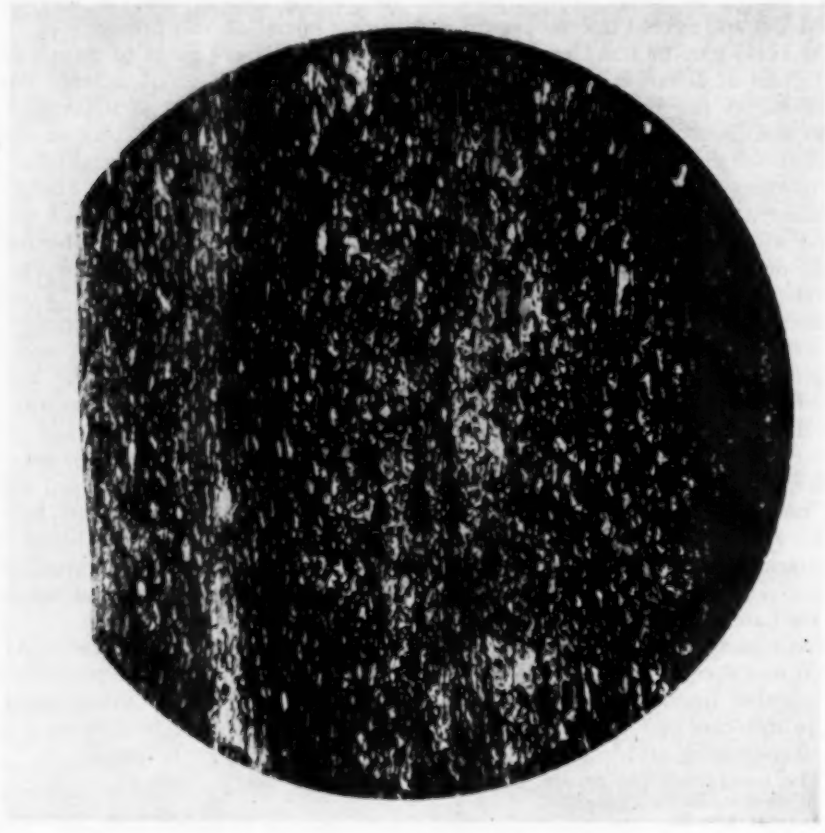

FIG. 1. Fragmentation of the elastic lamellae with the formation of vacuolated spaces. Note that the intima as well as the entire thickness of the media is involved. Weigert's elastic fiber stain.

A consultant in chest diseases, Dr. M. D. Bonner, was called at this time. His physical findings were much the same as Dr. Harrison's. He made three diagnostic punctures in the anterior part of the left chest. Two of these were made in the second interspace over the area of greatest tympany, in an attempt to measure any positive air pressure with a pneumothorax apparatus. The third puncture was made in the anterior axillary line in the area where tubular breathing was most marked. The puncture in the second interspace nearest to the midline (about 1½ inches from the left edge of the sternum) yielded neither blood nor air. The other two punctures yielded pure blood. The patient continued to get worse, so at 1 p.m. Dr. Bonner

aspirated between 400 and 500 c.c. of blood from the left chest. He got no air on this aspiration, either, despite the persistent tympany. The patient became progressively worse and died about 2:30 the next morning.

Necropsy Report. The body was that of a well-developed and well-nourished adult male. A tumefaction was present on the left side of the neck just above the clavicle which measured approximately 8 cm. in diameter and was elevated about 4 cm. above the surface. The external examination was otherwise not remarkable.

When the sternum was removed the pericardial connective tissue was found to

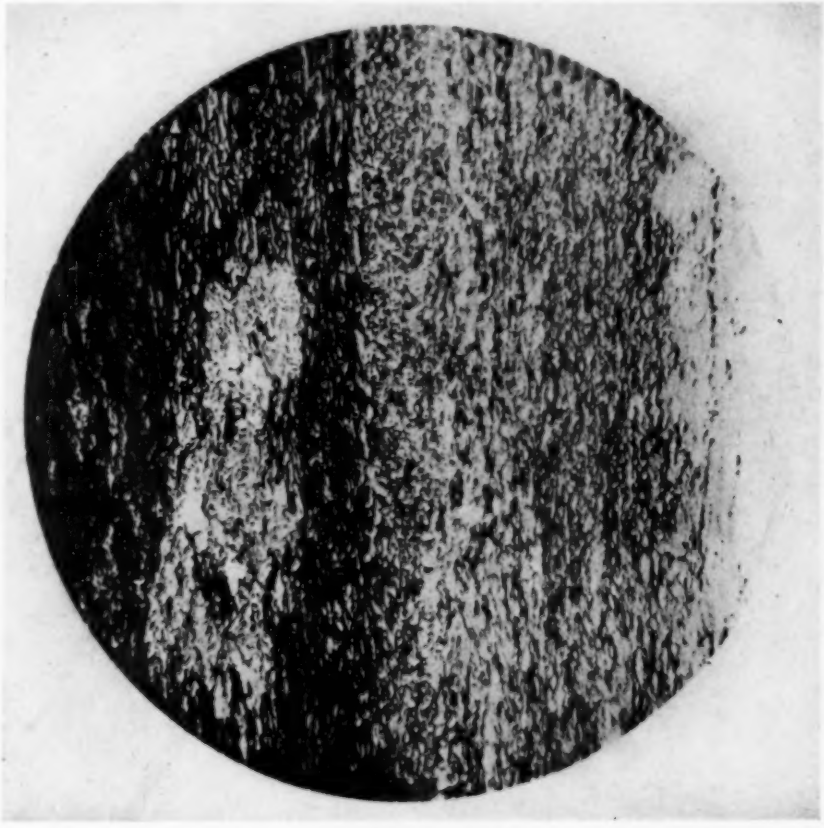

FIG. 2. "Medionecrosis aortae idiopathica cystica." The inner layer of the media shows marked degeneration with almost complete disappearance of elastic tissue. Weigert's elastic fiber stain.

be diffusely infiltrated with brownish black blood. This infiltrative process continued on either side of the pericardial sac, and in the hilar region of each lung dissected for a short distance beneath the pleura. Superiorly, the dissection continued to involve the loose tissue surrounding the aorta and extended upward to produce the tumefaction in the neck. Inferiorly, the same type of clot was seen to surround the aorta to the point of origin of the renal arteries.

The pericardial sac was incised and the epicardium and pericardium were found to be everywhere smooth and glistening, with no evidence of free blood.

The heart weighed 450 gm. and was without evident valvular lesion. At its

widest point the left ventricle measured 2.5 cm., and the right 0.8 cm. in thickness. A diffuse sclerotic process was noted in the coronary radicles and in several instances atheromatous plaques encroached to a considerable degree upon the coronary lumina.

Aortic atherosclerosis was of moderate degree and classical in distribution. There was no evidence of stellate or longitudinal wrinkling, nor were the vessels thickened or indurated. At a point 9 cm. from the aortic ring a transverse tear involving one-third of the circumference of the vessel was noted. Extending upward in an oblique direction and continuous with the first-described tear was a second vascular

FIG. 3. Incomplete rupture of the aorta with healing. A well defined scar unites the outer half of the media. Weigert's elastic fiber stain.

rent which involved two-thirds of the circumference. The entire thickness of the wall appeared to be involved. The torn edges were 0.8 cm. distant from each other at the widest point and the tear gradually tapered toward the ends. Brownish black clot formed the base of this crater and infiltrated in all directions therefrom.

The right pleural space contained about 750 c.c. of blood and blood clot, and a small amount of blood was noted in the left pleural space. The lower lobe of the left lung was completely atelectatic, as was the posterior three-fourths of the upper lobe. The anterior one-fourth of the upper lobe was crepitant and emphysematous.

The microscopic findings of interest were confined for the most part to the vascular system. Atheromatous plaques were numerous and advanced in the cor-

onaries, but the myocardium did not show significant degenerative or fibrotic changes.

Microscopic examination of the aortic intima revealed changes more extensive than were suspected in the gross examination. Sections stained with Scharlach R showed large lipoid deposits throughout the wall and a thickened fatty intima. Sclerosis was prominent, while in many areas young vascularized connective tissue and areas of myxomatous degeneration were seen. Atherosclerotic plaques were fairly numerous and in each instance medial atrophy was noted opposite the plaques.

FIG. 4. Intima at the point of rupture. Masson's trichrome stain.

Intimal thickening and fatty deposits were most marked in the immediate vicinity of the rupture.

Medial changes were present throughout the aorta and consisted for the most part of distortion and fragmentation of elastic lamellae (figure 1). Necrosis was both diffuse and localized, and in sections stained with hematoxylin and eosin, acellular areas filled with homogeneous basophilic material, with and without cyst formation, were present (figure 2). This picture is similar to that described by Erdheim [14] and others and called by them "Medionecrosis aortae idiopathica cystica." All layers of the media appeared to be affected equally with no predilection for the outer third; however, the degenerative changes were most marked in the region of rupture and

opposite the atherosclerotic plaques. In several instances medial scars were seen, with fibroblastic proliferation (figure 3).

The vasa vasorum of the adventitia were particularly interesting, in that they showed moderate arteriosclerosis throughout the extent of the aorta, while in the immediate vicinity of rupture the process was marked, with complete lumen obliteration, thrombosis and even recanalization.

The picture in the region of rupture was that of tearing without dissection (figures 4 and 5). In several instances, sections through the point of rupture included atherosclerotic plaques, but in no instance did the line of rupture course through one of these plaques.

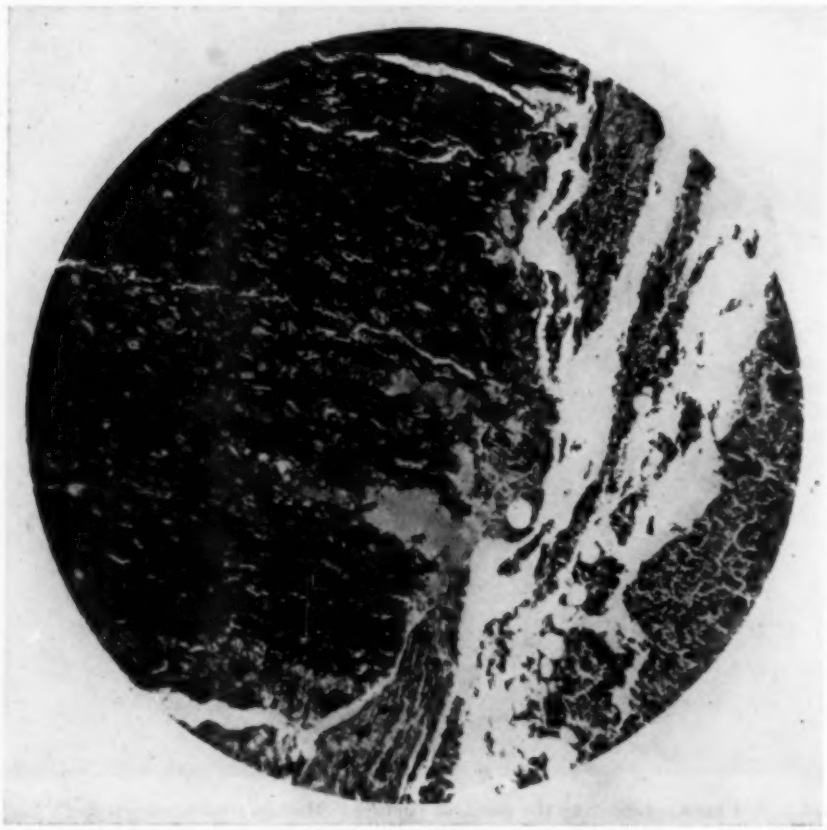

FIG. 5. Media at the point of rupture. There is no evidence of dissection. Areas of cystic degeneration are seen in the line of rupture. Weigert's elastic fiber stain.

PATHOLOGICAL COMMENT

From the above findings one can reason logically as to the histogenesis of rupture in this case. Degeneration of the outer portion of the media was in all probability due to ischemia, the result of adventitial arteriosclerosis. Middle and inner medial degeneration appeared to be secondary to atherosclerosis and injury to the vasa vasorum. The latter finding may be ex-

plained on the basis of increased intra-aortic pressure, as has been pointed out by Dill and Isenhour.[12] The presence of scars and evidences of repair suggested that the process had been of some duration. It is difficult to explain why the intimate vasculature of the aorta should be more involved at one point than at others, but this is a well-known feature of the disease and occurs in other organs. It is natural that rupture should occur in the area in which ischemia was most pronounced.

We do not propose that this mechanism is responsible for all cases of spontaneous rupture of the aorta. In many cases, especially in the young, one obviously must seek other etiologic factors. In some a necrotizing toxin has been frequently indicated, while in others infection cannot be eliminated.

It has been shown that healed medial scars are a not infrequent finding in routine examinations of the aorta. These may be the result of the healing of lesions which have the same etiologic basis as those which go on to rupture in other cases.

As Klotz and Simpson have suggested,[24] cases of spontaneous rupture of the aorta should be divided into two groups, those occurring in patients under 40, and those in patients above that age. In the younger group, the medial necrosis is of unknown etiology, but has been suspected to be of toxic or infectious nature. In the older group we are of the opinion that in most instances careful study will reveal degenerative vascular disease as the basis of the aortic lesions. We feel that in both groups the fundamental pathologic changes in the aorta are identical.

Clinical Comment *

At its onset this case was considered to be one of coronary occlusion. The rapid development of signs of fluid in the chest, however, excluded that condition and pointed to hemothorax. The tympanitic areas described strongly suggested the presence of air, in addition to the blood, in the pleural cavity. The roentgenologic findings and the results of needling, however, although positively establishing the existence of hemothorax, gave no evidence whatever of pneumothorax, and Dr. Bonner finally concluded that the tympany might be explained by compensatory emphysema of portions of the lung not collapsed by the hemothorax. In the light of the necropsy findings we now regard the increase of pain and the suffocative attacks in certain postures as due to pressure from blood clots on certain nerves and on the trachea. The pathogenesis of the peculiar sounds synchronous with the heart beat heard in the suprasternal notch seems worthy of special consideration. The "klunk," we believe, was made by the leakage of blood, and the friction sound we attribute to friction of the aorta against fibrin in the blood clots surrounding and pressing against it.

* Some months after the patient's death this case was discussed at a clinico-pathologic conference by Dr. Arthur Grollman, who made a definite clinical diagnosis of rupture of the aorta before the necropsy findings were revealed to him.

Etiology

This is obscure in the cases under discussion, i.e., those in which little or no gross change can be seen at the point of rupture. In some cases hypertension appears to be a predisposing cause, in others it is absent. Cases following minor trauma, effort or strong emotion may well be included in our group, and in such cases those factors may or may not be precipitating causes. Rupture of the aorta is more frequent in males, and in middle or later life, though a considerable number of cases have been reported in youth, and a very few in childhood. The age limits of cases collected from the literature by Achard and Paisseau [1] were 13 and 87 years. A number of cases have occurred during labor, as has already been noted. Kountz and Hempelmann,[25] and also Klotz and Simpson,[24] have reported cases following thyroidectomy in hypertensive patients.

Pathology

As Klotz and Simpson [24] point out, the storm center in discussions of the pathology of aortic rupture, with or without dissecting aneurysm, has been the question of whether such rupture can occur in an aorta with a perfectly healthy wall. Many have argued a priori that this is impossible. Others argued a posteriori that many ruptures had actually occurred in which skilled, even eminent pathologists could find no evidence of disease. However, in 1928 Gsell [19] attributed rupture to medial necrosis. In 1929, Erdheim [14] described a process, hitherto unrecognized, which he called medionecrosis aortae idiopathica, and in 1931 Cellina added a hitherto unknown form which he called medionecrosis aortae disseminata, an unusually diffuse form of necrosis of the media. In 1932, Moritz [31] confirmed Erdheim's findings, as have several others since.

Moritz describes medionecrosis aortae idiopathica cystica as a condition in which there is an increase in homogeneous, pale-staining, basophilic, acellular material in the media between the muscle cells and elastic fibrils. This may be found throughout the aorta, but is especially likely to be noted in the ascending arch. It is stained red with thionin, and light red or rose with cresyl violet R or polychrome methylene blue. It shows a distinct affinity for fat, and in one case showed an affinity for calcium. This condition was seen in slightly less than 10 per cent of adult aortas, but it was more marked in the three cases of rupture described by them. As these lesions progressed, they became cystic, and the chromatotropic substance lost its specific staining properties and became serous. Fat droplets, present in the early lesions, were absent in the cysts.

The essential underlying pathology, excluding factors such as atheroma, syphilis, major trauma and the various other conditions noted in our classification, appears to be the same, with or without the formation of a dissecting aneurysm, except for the element of time. If the rupture is sufficiently

gradual, a dissecting aneurysm forms; if not, it does not form. Many, perhaps most, authorities now believe that some form of medial necrosis, either Erdheim's or Cellina's type, is a prerequisite for "spontaneous" rupture as it is defined here. Cellina's type appears to be unique, but many observers, as stated above, have confirmed Erdheim's findings.

Grossly, the ruptures vary in size, location, form, direction and number. The size may vary from a mere puncture point to a tear several centimeters long. The location may be anywhere in the aorta, thorax or abdomen, but it is most frequent at or near the origin of the thoracic aorta and decreases in incidence distally. The form is usually a gaping slit, which may be clean-cut or irregular. Occasionally, however, a more or less circular hole is encountered. The direction of the rupture, when slit-like, may be longitudinal, transverse or oblique, some oblique ruptures involving the entire circumference of the aorta in a spiral. So far as number is concerned, a single rupture is the rule, but two or even three ruptures have been described. Multiple ruptures usually have been confined to the thoracic aorta, but in Brouardel and Vibert's case, already cited,[7] there was one rupture in the thoracic aorta and another in the abdominal. This case, it will be recalled, was the unique one with the paper-like thinness of the aortic wall.

When the rupture is intrapericardial, cardiac tamponade occurs. When it is extrapericardial, in the thorax, the blood may go into the mediastinal spaces and pleural cavities, and spread widely throughout the chest. In some cases in which the patient has survived several days, actual signs of healing of the initial stages of the rupture have been noted, and Ernst,[15] Fränkel,[16] Beneke,[4] and Schmorl[38] have reported complete healing of aortic rupture. Rupture into the pericardium is the most frequent type of rupture; Achard and Paisseau collected 66 cases (usually with dissecting aneurysm) of intrapericardial rupture, but only 19 cases of rupture into one or both of the pleural cavities. Rupture into the stomach with hematemesis, into the bronchi with hemoptysis, or into the peritoneal cavity is a rare event, and in the first two instances of these is usually associated with some extrinsic factor such as aortic syphilis, malignant invasion, etc. When death is practically instantaneous, it is probably due to ventricular standstill or fibrillation brought about by the shock of the rupture. In all other cases, if the rupture is intrapericardial, death is due to cardiac tamponade; if extrapericardial, to the massive hemorrhage.

Rupture into the left pleural cavity appears to be much commoner than rupture into the right; in Achard and Paisseau's series there were 16 cases of rupture into the left, two into the right, and one into both. This preponderance of rupture into the left side seems to be due to the fact that the aorta descends to the left of the spine. When rupture occurs in the ascending aorta, to the right of the spine, it is usually intrapericardial, and goes into neither pleural cavity. Enormous amounts of blood may be lost into a pleural cavity, such figures as 1420 c.c. (Achard and Paisseau[1]), 1700 c.c.

(Thoinot and Bernard [41]), 1800 c.c. (Brouardel and Vibert [7]), about 2000 c.c. (Gougerot [18]), and even the extreme figure of 3500 c.c. (DeAngelis [2]), appearing in the literature. In intrapericardial rupture, the limitation of the space plus the fatal effects of cardiac tamponade prevents such enormous losses, though Achard and Paisseau collected from the literature some remarkable figures, such as 640 c.c., 700 c.c., 800 c.c., 1000 c.c., and even 1500 c.c.

Symptomatology and Diagnosis

The symptoms occurring in spontaneous rupture of the aorta are of two main types. In the first type there is merely a terrific pain in the chest, back or abdomen; the patient gives a few gasps or convulsive movements and dies in a few moments. Clinical diagnosis is impossible in such a case. In the second type, the patient survives long enough to permit of physical examination, and often certain other procedures, such as roentgenologic study, that may lead to a tentative diagnosis, at least. It is often impossible to determine whether or not a dissecting aneurysm is present, though mathematical probability greatly favors its presence. If there is a history of two separate attacks of pain, the longer the interval between the two, the greater is the likelihood of a dissecting aneurysm's being present; but this rule is by no means infallible. Sometimes after the first pain due to intimal rupture, there will be more or less constant pain due to the dissecting process, with a final exacerbation of pain due to adventitial rupture and infiltration of the fibrous mediastinal tissue, if the rupture is extrapericardial. Extensive progressive spread of the area of pain, especially when it reaches high up in the neck or down into the abdomen, strongly suggests dissecting aneurysm, though the absence of such spread does not exclude it.

In patients surviving long enough, a train of symptoms develops which should suggest, sooner or later, the rupture of a large blood vessel, when the rupture occurs in the thorax. If the abdominal aorta is ruptured, the condition may be impossible to differentiate from rupture of some intra-abdominal viscus. As rupture of the abdominal aorta, apart from major trauma or syphilitic aneurysm, is exceedingly rare, we shall confine our remarks to intrathoracic rupture.

Most of the case reports prior to the present century describe a single prolonged episode of pain, whereas the more recent reports describe more cases showing two definite attacks of pain, separated by an interval in which symptoms are more or less in abeyance. We shall describe the latter type of clinical picture, as the former differs from it in no way save in the absence of the preliminary pain.

As Kaufmann [23] points out, rupture of the aorta is often a slow process. A small fissure may develop in the intima, due, perhaps, to some sudden increase in intravascular pressure, or merely to a giving way in the face of normal pressure, but the tearing of the other coats may proceed so gradually that no violent symptoms result until the adventitia gives way.

Discussing the duration of survival, Achard and Paisseau cite a large number of cases from the literature in which death occurred anywhere from a few seconds to eight days after the initial attack. As most of these were cases of dissecting aneurysm, however, we can hardly utilize them as the basis for conclusions as to the duration of life after the onset of a spontaneous rupture without such aneurysm. We can hardly be more definite on this point than to say that the patient may survive from a few seconds to a few days. It is natural to ask how anyone can survive more than a few seconds after rupture of the main arterial trunk of the body. There are two reasons for this survival: (1) the fact that, even without the formation of a dissecting aneurysm, the rupture may occur in stages; and (2) the fact that, in many instances, even after the adventitia ruptures, the rupture is so located that the blood can escape only into dense resistant mediastinal fibrous tissue or into the pericardial or pleural cavities, which quickly develop a positive pressure that decreases the rapidity of the blood loss.

The location of the pain is varied. In cases in which the rupture is into the pleural cavity the pain has been reported as thoracic, anginoid, in the side, in the back, in the abdomen, in the epigastrium, in the chin or jaw, etc. The pain appears to be due, not only to the rupture itself, but also to infiltration of blood into the dense cellular connective tissue around the aorta, to irritation of the pleura, etc. Abdominal pain may be due to irritation of the diaphragmatic pleura or occasionally to infiltration of blood along the aorta through the diaphragm down to the celiac area. Rupture into the pericardium may cause precordial, substernal or epigastric pain.

(Rupture of the abdominal aorta may show as its chief symptom severe intermittent pain in a testicle, as in Nicory's case [34] in which this symptom appeared at onset on the right side, cleared up during the night and recurred the next day, when the patient died. In other cases the pain may be intra-abdominal.)

Dyspnea may or may not accompany the initial pain, but as a rule it does not. Occasionally, as in Rose's patient,[37] it, rather than pain, may be the presenting initial symptom. It practically always occurs sooner or later, due to cardiac tamponade or massive hemorrhage.

The temperature may be normal, subnormal or elevated at onset, but it almost always rises to a moderate fever in patients that survive many hours. The pulse is usually rapid, but may be slow. An increase in the number of neutrophilic leukocytes usually develops very rapidly and reaches a high level, often 20,000 or more, within the first hours after the onset of symptoms, in contrast to the slowly developing and moderate leukocytosis found in association with coronary thrombosis.

Skerrett [40] described a unique physical sign in a case of rupture. His patient, a 71 year old man, collapsed while sitting on a water-closet. He was pale, unconscious and cyanotic, with no perceptible pulse. He took only short breaths at intervals. His heart sounds were feeble, but "also over the precordium there was a continuous adventitious sound which may be de-

scribed as gurgling or lapping, as of a cat lapping milk. This altered in character, the successive laps becoming more rapid and finally lost." It was totally independent of the heart sounds and quite different from any other sound Skerrett had ever heard in the chest, and suggested at once the leakage of blood. Skerrett thought that the heart muscle had ruptured but necropsy showed that a dissecting aneurysm had ruptured into the pericardium.

To sum up, the cardinal symptoms of spontaneous rupture of the aorta are intense pain, usually thoracic, anteriorly or posteriorly, sometimes abdominal; dyspnea; collapse; and evidence of either cardiac tamponade or of the rapid accumulation of blood elsewhere in the thoracic cavity, or in the abdomen, if the abdominal aorta is ruptured. Often this picture is preceded for hours or days by an initial pain which may be slight or severe, but which usually subsides in part, at least, to be followed by the final major symptoms.

There is no special pattern to the pain. Its varied location has already been mentioned. Its intensity may vary from slight to agonizing, except in the final adventitial rupture, when it is of almost unique intensity.

Most of these cases are erroneously diagnosed as coronary occlusion at their onset, as was our case. The rapid accumulation of fluid in the chest, when the rupture is extrapericardial, will reveal this error in time. In intrapericardial cases the diagnosis is more difficult; for even when two separate pains occur, the first one may resemble an ordinary anginal attack very closely. When leakage into the pericardium is slow, a paradoxical pulse is likely to develop. When either Harrison's or Skerrett's sign is present, a correct diagnosis may be possible. The high leukocyte count developing within a few hours after adventitial rupture is against coronary occlusion. As has already been mentioned, a progressive extension of the pain, especially into the lower abdomen or upper neck, is strongly indicative of a dissecting aneurysm with impending rupture of the aorta and the occurrence of intermittent signs of aortic insufficiency is also highly suggestive of the condition. The absence of these findings, however, does not invalidate the diagnosis. Normal electrocardiographic findings or evidence of simple left axis deviation are to be expected in aortic rupture with or without dissecting aneurysm. When hemothorax causes marked cardiac displacement the electrical axis may shift accordingly. Respiration does not increase the pain of coronary occlusion.

Treatment

This can only be directed towards relieving the agonizing pain of what is inevitably the patient's final illness, and consists of large and frequently repeated doses of morphine or some similar drug, as needed.

Summary

1. Rupture of the aorta is by no means infrequent in the anatomical, as well as the pathological and clinical literature.

2. It occurs without the formation of a dissecting aneurysm more often than is usually realized, though the cases with dissecting aneurysm are much more numerous.

3. The literature on the type of rupture occurring without dissecting aneurysm has been reviewed and an additional case of our own presented, with clinical and pathological findings.

4. The gross and microscopic pathology of the condition is discussed.

5. Certain diagnostic criteria, including a hitherto undescribed physical sign, have been suggested.

6. The prognosis is hopeless and treatment is purely symptomatic.

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AN EVALUATION OF THE DARK TEST*

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Introduction

Over 40 methods and apparatus have been described in the past 85 years, claiming to measure the time necessary for the eye to become accustomed to low illumination (scotopic vision). Delayed dark adaptation (dysaptation) has come to be considered minimal or subclinical night blindness (hemeralopia). Of academic interest at first, the changes in the manner of living and lighting in this century have produced new demands upon adaptation ability and new interest in this phenomenon. Then, too, new impetus for study appeared following the claims that lack of vitamin A was the specific deficiency of night blindness, xerosis and xerophthalmia (Pillat, 1929–1940; Tassman, 1932). As a result of these and other studies it was assumed that the lack of vitamin A was responsible for poor dark adaptation.

Reports of dark adaptometry have been numerous (Wosika, 1943). Many workers have stated that large blocks of the population showed poor dark adaptation. Further, their results have shown that the administration of vitamin A improved this vision at low luminosity and on this basis have recommended, enthusiastically, massive doses of vitamin concentrates for all people. Other workers, although dubious of existing methods, have agreed in principle and have offered modifications or new apparatus for the dark test. Still others have found no relationship between dysaptation and vitamin A.

The present work was undertaken to establish, if possible, the reliability of the Bio-photometer. There can be no question that the machine measures the perception of dim light. This it has in common with all adaptometers. However, when the attempt is made to translate the results into a chemico-physiologic process concerning vitamin A, great difficulty is encountered.

The present war emergency would seem to make this report timely. Practically, it would be of great importance to be able to find and correct delayed visual adaptation to low illuminations, particularly since the occurrence of dimouts and blackouts. Theoretically, a certain percentage of accidents in the air and on the highway might thereby be eliminated.

Procedures

For this study 700 ambulatory patients were taken at random from the clinics of Northwestern University Medical School. Patients found with poor dark adaptation were examined by ophthalmologists and rejected if local disease of the eye was disclosed. Conditions such as retinitis pigmentosa were not included in the series.

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The patients were between 15 and 78 years of age, the average being 45.5 years. There were almost twice as many women as men. Members of the colored race numbered 84; their average age was slightly over 39, whereas the whites averaged over 46 years.

Medical students, young physicians and various workers from the clinic personnel (80) were used as controls. They constituted a superior group from the economic and intellectual standpoints. They were all of the white race, averaging 26 years, and were without obvious defects.

The instrument used was the Bio-photometer which consisted essentially of a metal box in which a constant source of strong light as well as a much weaker light emanated. The intensity of the weaker light was controlled by a rheostat with the resistance calibrated in millifoot candles. Between the eyepiece and these lights there was interposed a metal screen perforated in the form of a quincunx. The greater resistance to light through these perforations was from right to left. When the rheostat was turned to the right (clockwise) the spots faded. When turned left until the central spot appeared the end point was reached and this point was recorded. The whole screen could be lowered so that the bright source of light reached the eyes unimpeded and was used to exhaust the visual purple.

The technic used was similar to the one reported by Jeans, Blanchard and Zentmire (1937). During the test, the subject was questioned as to diet adequacy. Information on foods high in vitamin A, such as milk, eggs, butter, cheese and leafy green vegetables was specifically noted. No attempt was made quantitatively to resolve the number of international units of vitamin A, since no great accuracy was possible except on theoretical grounds. Workers who have had experience in attempting to evaluate diet histories (Elder and Emery, 1937) will readily understand the difficulties of securing truthful complete histories of foods consumed. In addition, it has been shown that the various common foods vary from season to season in their vitamin A content (Dornbush, Peterson and Olson, 1940). Further, far reaching dietary surveys have shown "that diets which meet the average minimum requirements in other respects furnish in the neighborhood of from 3,000 to 6,000 international units of vitamin A per day to adults." This must be considered adequate when the "minimum requirement" for adults is approximately 2,000 to 2,500 international units per day (Daniel and Munsell, 1937). Therefore, the diets were judged to be sufficient or insufficient, on a qualitative basis. These estimations were made without the knowledge of the dark test results and since one observer made them all, any bias will be equitably reflected throughout the entire series.

Results

The results of the study are reported in the following tables and graphs.

Table 1 showed for 668 patients the number and percentage of normal, borderline and abnormal Bio-photometer readings occurring with normal (10

TABLE I

The number and percentage of normal, borderline, and abnormal Bio-photometer readings occurring with normal and deficient diets on 668 patients. (Compare with the control series in table 3.)

Bio-photometer Readings	Type of Diet			
	Normal (10%)		Deficient (90%)	
	Number	Per cent	Number	Per cent
Normal	14	20	94	16
Borderline	17	24	138	23
Abnormal	39	56	366	61
Totals	70	100	598	100

per cent) and deficient (90 per cent) diets. Of those considered on suitable intakes 20 per cent of 70 patients were normal, while 16 per cent of 598 patients were normal when the dietary intake was inadequate. Table 2 showed the same data rearranged into a four-fold table. Here the observed frequencies were very close to the expected frequencies. Since the chi-square

TABLE II

Four-fold table of 668 patients showing observed and theoretical (in small box in upper corner of each cell) frequencies of normal and abnormal Bio-photometer readings with normal and deficient diets. Chi-square = 0.84.

	Bio-photometer Readings		Totals
	Normal	Borderline and Abnormal	
Normal Diet	11.4 14.0	58.6 56.0	70.0
Deficient Diet	96.6 94.0	501.0 504.0	598.0
Totals	108.0	560.0	668.0

equaled 0.84, the probability equaled about 0.40, which means that about 40 times in 100 chance operates in this association (Pearl, 1940; Davenport and Ekas, 1936).

The results of 80 controls (table 3) showed the number and percentage of normal, borderline and abnormal Bio-photometer readings occurring with normal (30 per cent) and deficient (70 per cent) diets. Of 24 subjects considered to have a normal diet, 79 per cent showed normal Bio-photometer

TABLE III

The number and percentage of normal, borderline and abnormal Bio-photometer readings occurring with normal and deficient diets on 80 controls.

Bio-photometer Readings	Type of Diet			
	Normal (30%)		Deficient (70%)	
	Number	Per cent	Number	Per cent
Normal	19	79	41	73
Borderline	4	17	13	23
Abnormal	1	4	2	4
Totals	24	100	56	100

readings, and 75 per cent of 56 subjects having a deficient diet were normal in adaptometer ability. These data were rearranged into the four-fold table shown in table 4. Here the observed normal Bio-photometer readings were shown and the borderline/abnormal were combined for the sake of simplicity. This first attribute was compared with the presence or absence of a normal diet. The theoretical frequencies were computed on the basis of the prob-

TABLE IV

Four-fold table of 80 control subjects showing observed and theoretical (in small box in upper left corner of each cell) frequencies of normal and abnormal Bio-photometer readings with normal and deficient diets. Chi-square = 0.31.

	Bio-photometer Readings		Totals
	Normal	Borderline and Abnormal	
Normal Diet	18.0 19.0	6.0 5.0	24.0
Deficient Diet	42.0 41.0	14.0 15.0	56.0
Totals	60.0	20.0	80.0

ability theory and placed in the cells in the small box in the upper left corner. It was noted that in each instance the observed frequencies were almost identical with the theoretical frequencies. This would indicate that the presence or absence of either attribute did not influence the presence or absence of the other. The calculation of the chi-square equaled 0.31 and the probability equaled more than 0.50. Any association existing between

diet and Bio-photometer readings was extremely small since chance operated in more than 50 of 100 instances.

Although men were known to suffer from night blindness with greater frequency than women, the dark test showed no distinction between the sexes. Men showed 18 per cent normal and 82 per cent borderline/abnormal readings. Women showed 16 per cent normal and 84 per cent borderline/abnormal dark test readings. The Bio-photometer readings of men varied slightly

TABLE V

This table compares whites (616 patients) with negroes (84 patients) as regards the Bio-photometer performances.

Bio-photometer Readings	Race			
	White (88%)		Negro (12%)	
	Number	Per cent	Number	Per cent
Normal	92	15	26	31
Borderline	137	22	21	25
Abnormal	387	63	37	44
Totals	616	100	84	100

regardless of diet adequacy. Thus, 21 per cent were normal where the diet was considered sufficient and 17 per cent were normal where the dietary standards were low. Women had a slightly decreased number of normal readings on deficient diets, 13 per cent as against 20 per cent normal readings when the diet was adequate.

Since pigmentation had been considered a factor in the utilization of vitamin A, table 5 was constructed comparing race as regards dark test

TABLE VI

This four-fold table compares the effect of race upon Bio-photometer readings on 700 patients. Chi-square = 13.53.

	Bio-photometer Readings		Totals
	Normal	Borderline and Abnormal	
White	103.8 92.0	512.2 524.0	616.0
Negro	14.2 26.0	69.8 58.0	84.0
Totals	118.0	582.0	700.0

ability. Over twice as many negroes had normal Bio-photometer curves (31 per cent for negroes; 15 per cent for whites). That this increase is real is borne out by table 6. Pigment may be a factor since fewer whites had normal dark adaptation than were expected from the theoretical standpoint. However, almost twice as many negroes had normal dark adaptation as were calculated possible on the basis of a complete independence of these occurrences. Chi-square equaled 13.53 which meant that there was far less than one time in 100 that chance affected negroes' superior dark test ability when compared to whites'.

Several disease processes had been considered to be responsible for poor dark tests. Since there were no diagnosed cases of cirrhosis of the liver or ulcerative colitis among the patients tested, a comparison was made with

TABLE VII

In this table an attempt is made on 679 patients to calculate the effect of blood pressure upon Bio-photometer readings. Chi-square = 24.36.

	Bio-photometer Readings		Totals
	Normal	Borderline and Abnormal	
Low/Normal Blood Pressure	85.2 / 107.0	404.8 / 383.0	490.0
High Blood Pressure	32.8 / 11.0	156.2 / 178.0	189.0
Totals	118.0	561.0	679.0

the readily available blood pressure determinations. There was a distinct decrease in the normal readings for the hypertensive group (6 per cent) as compared with the normal (21 per cent). This difference seemed significant. Great discrepancies were found between the actual and calculated values. Although more individuals (among 679) were found to have normal dark tests with normal blood pressure readings than were considered possible theoretically, only one-third of the calculated number was observed in the hypertensive group (table 7). Since chi-square equaled 24.36, there were almost a million and a half chances to one the blood pressure levels somehow influenced the Bio-photometer results.

It is known that the incidence of hypertension increases with age. This is true in the present study.

Figure 1 depicted the spread of normal and borderline/abnormal dark tests throughout the various decades. The great increase in poor adaptometry with advancing years was apparent. Table 8 showed that normal

dark tests occurred more frequently under 40 than were calculated to be possible up to the age of 40. After this time the drop in the number of normal dark tests was great. Chi-square equaled 104.9 which made the association significant (probability equaled less than 0.01).

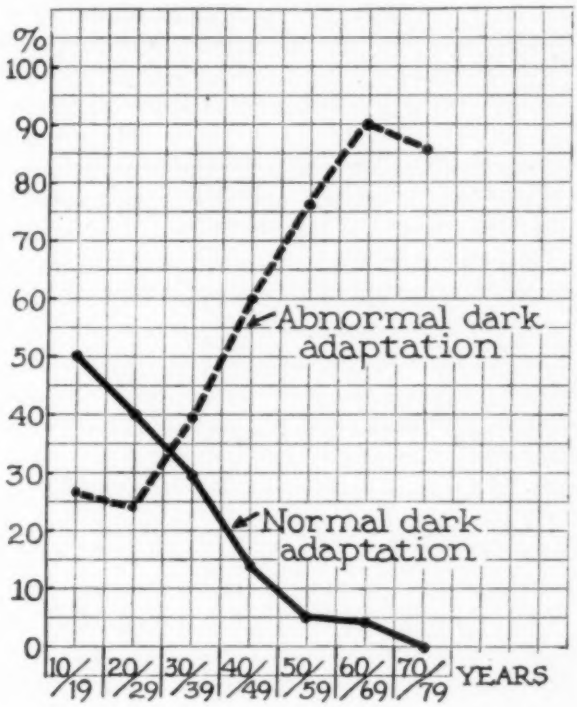

FIG. 1. Graph showing the incidence of normal and abnormal Bio-photometer readings for seven decades on 700 patients.

The possibility of quantitatively and qualitatively decreased diets with increasing age should be considered. In the present series in the advancing years no more deficient diets could be found than among the younger age groups.

DISCUSSION

The work of Hecht (1920), Fridericia and Holm (1925) and Wald (1935) was of fundamental importance in linking visual purple to light perception and vitamin A, notwithstanding the criticisms of Krause and Sidwell (1936) and Granit et al. (1939). The work of Popper (1940) may serve to strengthen this relationship. Theoretically the dark adaptation test should form a yard stick for the measurement of vitamin A deficiency, although Wessely (1916) cautioned that there was danger in assigning numbers to the dark test.

TABLE VIII

Theoretical (left upper corner of each cell) and observed frequencies of Bio-photometer readings (normal and abnormal) for seven decades. Chi-square = 104.9.

Age in Years	Bio-photometer Readings		Totals
	Normal	Borderline and Abnormal	
10–19	5.7 17	28.3 17	34
20–29	12.3 29	60.7 44	73
30–39	22.0 38	108.0 92	130
40–49	30.0 23	148.0 155	178
50–59	23.8 7	117.2 134	141
60–69	18.0 4	90.0 104	108
70–79	6.0 0	30.0 36	36
Totals	118	582	700

There can be no quarrel with the attempts to discover subclinical vitamin A deficiency. The natural impulse is to accept and to further observations dealing with such a fundamental problem as the nutritional state of the population. The method or methods used are immaterial. The results are important and the therapeutic possibilities of unsuspected insufficiencies challenge all workers for health to coöperative effort. The question at issue, then, is socioeconomic, as well as medical.

The many apparatus designed for resolving visual ability in dim light into figures are all similar, and this fact precludes any claim of specificness.

Innumerable reports have appeared, hastily confirming the contention of Jeans that vitamin A deficiencies are common. Actually, vitamin A deficiency was certain to be suspected in approximately one-half of the persons subjected to dark adaptation tests since to establish a normal average in any group of persons examined, a certain percentage must be found below as well as above this average.

A series of papers has appeared purporting to show the plausibility of the test on theoretical grounds. These authors devised new machines which they believed were improvements on existing apparatus (Hecht, 1939, Sloan, 1939 and others).

Then, too, other papers have been critical of the value of the test. The reasons are numerous: the lack of correlation of diet, increased or decreased vitamin A intake, blood vitamin A and carotene levels with the dark test values. The training factor, mentality, age and individual differences have been advanced as causative agents of discrepancies in the supposed state of nutrition and mild degrees of night blindness.

The present results are interesting from the standpoint of the large series (780 adults) studied. Comparing the control series with the patients, there would seem to be no doubt that the Bio-photometer reflects a higher percentage of normal readings in the former group. Thus, eliminating for the moment all considerations of the mechanical accuracy of the apparatus, it is seen that for the control series 75 per cent are normal, 21 per cent are borderline and 4 per cent are abnormal, whereas for the 700 patients 17 per cent are normal, 23 per cent are borderline and 60 per cent are abnormal. The conclusion from these figures that the control group is quite superior in the dark test seems to be justified. This has been found to be true in other clinics where similar studies have been made.

Therefore, factors have been sought which might account for this difference. Better food habits according to present standards of dietary intake were considered likely and information upon the present series revealed that for the control group 30 per cent of the individuals were on normal diets, whereas 70 per cent were deficient. The patient series viewed similarly showed only 10 per cent on normal intakes, whereas 90 per cent were on insufficient intakes. If, then, no further analyses are made, it may be assumed that dark adaptation tests are more likely to be normal in control patients whose dietary intake is superior. This has been done repeatedly in the literature.

The present study, however, enabled a more detailed division of the material, and it became apparent at once that when the Bio-photometer readings were considered for the group of controls, 70 per cent and 73 per cent were normal when the diet was normal, or deficient, respectively. The patient series showed 20 per cent and 16 per cent normal readings on normal and deficient diets respectively. Therefore, on the basis of a qualitative examination of food habits, diet alone can not be considered an influential

factor upon the dark test. The statistical treatment of these data showed that the observed and theoretical frequencies were so close that the chance of diet influencing the Bio-photometer readings was almost nil.

Although the practice factor was considered very important, particularly in the examination of children, this was not apparent in the present series of adults. Occasionally patients were encountered who were unable to follow simple instructions, and these readings were discarded immediately. Practically the same percentages were found, whether or not more than one test was performed.

Clinical night blindness always has been reported with greater frequency in men than in women and the greater exposure of men to sunlight had been considered to be the cause (Aykroyd, 1930). In the present study there were no essential differences between men and women.

Since visual purple is a pigment, several attempts have been made to correlate general pigmentary changes with dark tests. Even blondes, brunettes and red-heads have been compared by Getz et al. in 1939. In this series, negroes were found to have better adaptation than whites. There was, however, no increase in normal dietary intake in the colored race over the whites. There was a difference in ages, the negroes being the younger. Whereas earlier reports favored the view that pigmentary changes influenced adaptometer results, Birch-Hirschfeld (1917) and Birnbacher (1927) reported no relation of hair or eye color to dark test ability. Bunge and Heyn (1938) reported that adaptometer tests in eight cases of albinism showed curves similar to the pigmented controls.

Numerous attempts have been made to link poor adaptometer performances with diseases and other processes. Disease of the liver (cirrhosis), endocrines (hyper- and hypothyroidism), ulcerative colitis, pregnancy, etc., all have been made responsible for poor dark tests. In these routine clinic patients, unchallengeable diagnoses could not be made of such definite clinical syndromes with great enough frequency to permit statistical comparisons. It was not doubted that among the patients studied some degree of cirrhosis might be present.* Definite diagnoses of cirrhosis did not occur, however, and, therefore, no figures could be obtained comparable to the works of Park (1935, 1936), Haig, Hecht and Patek (1938), Feldman (1938), Patek and Haig (1939).

Blood pressure determinations were available on almost any series of patients. Since this represented chronic disease, the attempt was made to compare the dark test and blood pressure readings. Surprisingly enough, this association was found to be close. There was about one million and a half to one chance in favor of the relationship. In other words, it appeared extremely likely that blood pressure levels affected Bio-photometer readings.

Further analyses on this present group revealed that age carried with it

* It is interesting here to speculate upon the effect of age and changes in the liver. Schnitker and Hass (1934) found that 36 per cent of patients averaging 52 years of age at death had at least microscopic changes in the liver.

an ever increasing liability to hypertension. In addition, it was discovered that the incidence of normal and deficient dietary intakes remained practically the same throughout the various decades. Now, a further correlation remained to be made between the dark adaptation test and age. This association was significant. Restated, this meant that dietary factors (vitamin A) had no influence upon Bio-photometer readings but that age was most important. The older the individual, the less likely were his chances of having a normal dark adaptability.

The literature contained numerous references to the age factor and vision in dim light. Although Selling (1939) was of the opinion that the glare sensitivity did not increase with age, most workers who had tested adults for dark adaptation concluded that age definitely increased the threshold for dim light. However, where further comment was made, the occurrence usually was dismissed lightly. Hecht and Mandelbaum (1939) stated that "there is a subtle shift in distribution of rod thresholds with age which deserves to be pointed out, but we lay no emphasis on it." They considered that a possible yellowing of the ocular media with age accounted for the more obvious change in the final cone threshold. It should be remembered that these authors were only reporting on a group of 110 university associated persons. Lindquist (1938) concluded that different standards should be set up for the various age groups, since his older individuals showed poorer adaptation ability. Ferree, Rand and Lewis (1934) and Ferree and Rand (1933, 1936) concluded that for best efficiency, workers should be segregated into groups by ages, so that light intensities might be increased more easily. Older individuals needed more light "to keep pace with the failing powers of the eye."

This was confirmed by the present work and agreed with the report of Birch-Hirschfeld (1916) who found among 300 patients examined the following distinct increase of disturbed dark adaptation values: first and second decades 11.6 per cent deficient, third decade 20 per cent, fourth decade 26 per cent and fifth decade 35 per cent. He mentioned sclerosis, coloring of the lens with age or possibly some occurrence within the retina as possible explanations.

Local diseases of the eye were ruled out in the present series and in many of the published reports. In addition, the changes in the visual ability seemed to play no part in this aging process, since refractive errors were found to have no effect upon the ability to perform the test.

The present material was reëxamined to determine, if possible, if age accounted for the difference between the controls and the patients in dark test ability. The average age of the controls was 26 years and 75 per cent were normal. Inspection of figure 1 showed that only 40 per cent of the patients were normal in the third decade. Thus, the controls were considered definitely superior in their ability to perform the test regardless of age. Simple individual variations were responsible for most of these better performances.

An analogy may be drawn with an individual's ability to shoot straight. Given identical weapons and firing conditions, people will be found to vary tremendously in marksmanship. These same factors may be operating in the case of dark adaptometry. Kyrieleis (1938) remarked that strong and weak lightnesses were relative notions whose absolute values varied within markedly wide limits from person to person. These individual variations must play a large rôle in the reports in which children between narrow age limits were tested.*

Another factor had been considered to be heredity. Habs (1938) approached this problem by a study of adaptometry in 20 identical and 20 non-identical twins. He found that the curve was very similar for identical twins, more so than for the other group. This he considered as proof of the inheritance of dark test ability. He raised the question of environmental and vitamin A factors but drew no conclusions. Wood (1938) stated that the Birch-Hirschfeld photometer was satisfactory for dark tests. Further, he felt that both vitamin A deficiency and strong light were necessary to produce night blindness. However, he was aware that not all individuals subjected to the same conditions became night blind. He attempted to explain this on the basis of heredity.

Recently the nervous system was mentioned as a factor in the adaptation process. Thus, Elsberg and Spotnitz (1938) reported that the time required for adaptation was dependent upon the rate of recovery in the nervous system from previous lighting. Schouten and Ornstein (1939), after excluding all purely physical or chemical possibilities, were led to the assumption that the retinal synapses had a part to play in the adaptive process. Lythgoe (1940) ingeniously suggested that a spread of synaptic connections might occur as dark adaptation proceeded. This tended to decrease finer discriminatory sensations.

The effect of vitamin A deficiency upon the nervous system is still in dispute. However, it was shown that oxygen affects the nervous system and the adaptation curves (Fischer and Jongbloed, 1936; McFarland and Evans, 1939; McDonald and Adler, 1939). Nagel's adaptometer had been used to show a direct proportion between the amount of hemoglobin and the dark test in 10 healthy and 11 anemic patients (Takayasu, 1934).

Frequently, pupillary width was mentioned as a factor in aiding dark adaptation. Mention should be made of the work of Phillips (1939) who found that a comparatively large pupil in the light or dark or both retarded the test. He stated: "Since there is a significant decrease in pupil diameter in the light with age, the slowing of the course of dark adaptation with age cannot be due to pupil variations. Pupil diameter in the dark also decreases

* It was interesting to consider in this connection the work of Harris and Abbasy (1939) who employed the Birch-Hirschfeld photometer. They reported the following readings on poor children between the ages of 11 and 13: 43 per cent "normal," 34 per cent "slightly below normal," and 23 per cent "definitely subnormal." The present work with the Biophotometer for the age group between 10 and 19 years showed: 50 per cent normal, 23 per cent borderline and 27 per cent abnormal. These results do not differ significantly.

with age." Sloan (1940) felt that accurate correction factors should be applied for pupil width in dark adaptation.

Fatigue undoubtedly played a part in dark tests. Wiersma (1901, 1902) studied the effects of fatigue on minimal impressions and found that attention fluctuated widely. He reported that low grade lights may be perceived on straining but these tended to disappear and to recur on further straining. Because of previous training, he found some persons able to perform better in the morning and others at night. Older persons showed fatigue fluctuations in wider ranges than younger persons. Wiersma explained his findings by postulating that the cause (*a*) might be nerve fatigue, (*b*) might be a tiring of the muscles of fixation and accommodation which permitted a new less sensitive part of the retina to be stimulated by light, and (*c*) might be central. In 1908, Rabinowitsch proved the effect of fatigue (increased previous lighting) upon the curves obtained with Nagel's adaptometer. The recent widespread interest in the fatigue phenomenon will undoubtedly confirm these old facts and bring new ones to light.

Birnbacher (1927) used Birch-Hirschfeld's apparatus and checked each test upon himself. He found that he varied so much from day to day that he cautioned against too exact interpretation of results. In this connection, it was interesting to speculate upon the laws of chance. As Jung (1938) pointed out: "Using an instrument whose readings are affected by large chance errors, an investigator examines, say, 100 subjects. He selects the 10 people whose performances on the test happen to be the poorest, and gives them some kind of treatment. Next day he reëxamines the 100 subjects. The average performance of the 100 is exactly what it was the day before, but the 10 who did most poorly then are now found to have improved strikingly." Thus, in any test where great variability existed, the lowest performers tended to improve with repetitions and similarly, the highest performers tended to gravitate toward the mean. Jung suggested the name "centripetal drift" for this phenomenon of regression toward the mean.

It became necessary, then, to consider the test itself in an attempt to explain the discrepancies between the various workers in the field. It was apparent that there were two main measurements of the test. One concerned the ability of the eye to adapt itself to dim light and the other was the rate of this adaptation process. It was to this latter factor that most attention had been directed. Yet, there was published work to prove that the rate of dark adaptation was no function of vitamin A in the body (Hecht and Mandelbaum, 1938; Wald, Jeghers and Arminio, 1938; Lewis and Haig, 1939, 1940). These same workers had shown changes in the final rod threshold for minimal lighting to be dependent upon the vitamin A intake and reserves. Since even this had been questioned by other workers, notably Steffens, Bair and Sheard, 1939; Isaacs, Jung and Ivy, 1938, 1940, who were unable to confirm the claims of the above observers, the final answer on the question of the linkage of vitamin A and the dark test must remain open.

As concerns adaptometry, there can be no questions. The test measures the rate of dark adaptability of eyes but only with fair accuracy. This rate is dependent upon many factors as enumerated above: individual, hereditary, mental, nervous system qualifications dependent upon inherent abilities, oxygen consumption, retinal synapses, etc., and all of these factors change with age tending to become less acute with increasing years. This natural wearing out process has been remarked for many bodily functions. It has been assumed frequently that this rate of adaptation is a function of vitamin A, but proof for this point has not been produced. With so many variables, the use of the rate of adaptation alone as a measure of vitamin A in the body would seem to be in its simplicity highly optimistic.

Summary and Conclusions

1. The literature concerning the dark adaptation test divides into three groups:

a. Authors who believe that delayed dark adaptation as measured by existing instruments means deficient vitamin A in the diet, in metabolism, or in the reserves of the body.

b. Authors who, using the same apparatus, find no correlation between vitamin A and the recorded ability to perform the dark test.

c. Authors, dubious of the positive correlation between vitamin A and performance on existing photometers, who have offered modified apparatus of their own.

2. The 700 ambulatory patients are random selections averaging 45.5 years.

3. The 80 controls are healthy adults (medical students, etc.) averaging 26 years.

4. Local ophthalmological conditions are excluded in all subjects. Thus, where present, poor dark tests are considered examples of so-called "essential hemeralopia."

5. Bio-photometer readings show:

a. The training factor to be negligible;

b. A higher percentage of controls having normal dark tests than patients but this could not be ascribed to a superior dietary intake;

c. Normal adaptation in higher percentage of patients receiving normal qualitatively estimated diets, though no strong association could be established statistically;

d. Sex has no effect upon vision in dim light whether diets are normal or deficient;

e. Negroes are significantly superior in dark test performances (average age of negroes less than whites);

f. Patients with hypertension exhibit a significantly higher percentage of poor dark tests;

g. Increasing age influences dark adaptometry adversely.

6. The effect of various factors upon the dark test are discussed:

a. Negatively, vitamin A and the diet, sex, race and the training factor:

b. Positively, individual factors of age, mentality, fatigue, heredity, inherent abilities of the nervous system (oxygen consumption, retinal synapses, etc.).

7. Recommendations are made that further work with the rate and end values of dark adaptation (both rods and cones and nervous system influences) be performed to establish the physiologic basis for the test rather than accepting previous work on the importance of vitamin A.

8. A correction factor for age must be determined and applied in future work with adaptometers.

9. In the present state of knowledge of scotopic vision, the terms night blindness and poor dark adaptation tests should not be used synonymously.

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THE EFFECT OF CERTAIN ANTACIDS IN MAN MEASURED BY A SIMPLIFIED METHOD FOR THE CONTINUOUS RECORDING OF GASTRIC pH *

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In a previous communication [1] we described a method for the continuous recording of gastric pH in man. At that time we were of the opinion that colloidal aluminum hydroxide † in 30 c.c. dosage made up to 200 c.c. with water, or 200 c.c. of milk alone, fulfilled the physiological criteria of an ideal antacid. It was also noted that the use of calcium carbonate or of magnesium salts caused a great initial rise in pH but that their buffering effect was of short duration.

In the present study we have extended our observations on antacids with the use of an improved method for the continuous recording of gastric pH. In the procedure as originally described a tube at least 5/16ths of an inch in diameter containing a glass electrode and accessory tubes was introduced into the stomach. It was necessary that the patient retain the tube during the entire period of observation. Another disadvantage was that this arrangement required frequent recementing of the glass electrode at the bottom of the stomach tube to avoid electrical leakage.

Method

The mechanical difficulties previously encountered have now been obviated by leading gastric juices from the stomach by means of a No. 16 French duodenal tube to a standard commercial continuous flow electrode. This electrode is coupled with a Beckman pH meter and with the recording potentiometer and the pumping system which have previously been described.[2, 3, 4] Thus, only standard commercial equipment available on the open market was utilized.

A series of patients with gastrointestinal symptoms was studied on repeated occasions by the above method. Patient E. B., who had a duodenal ulcer, was used as a subject on five successive mornings and the findings in this series of experiments were typical. The effect of sodium bicarbonate 1 gm., calcium carbonate 1 gm., 200 c.c. of sweet milk, 200 c.c. of milk plus calcium carbonate 1 gm., and colloidal aluminum hydroxide 15 c.c. plus milk of magnesia 4 c.c. was studied. The patient's fasting gastric juice was removed and adjusted to a pH of 1.5, after which 35 c.c. were returned to the stomach as the control specimen. This specimen was cir-

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† The preparation amphojel was used.

culated around the electrode by means of the pumping system and a control tracing was made on the recording potentiometer. Then the various substances to be studied were added in 200 c.c. volumes.

Results

Figure 1 was made by superimposing the tracings obtained on the above patient on five successive mornings.

It will be noted from this figure that 15 c.c. of colloidal aluminum hydroxide plus 4 c.c. of milk of magnesia when added to 200 c.c. of water act

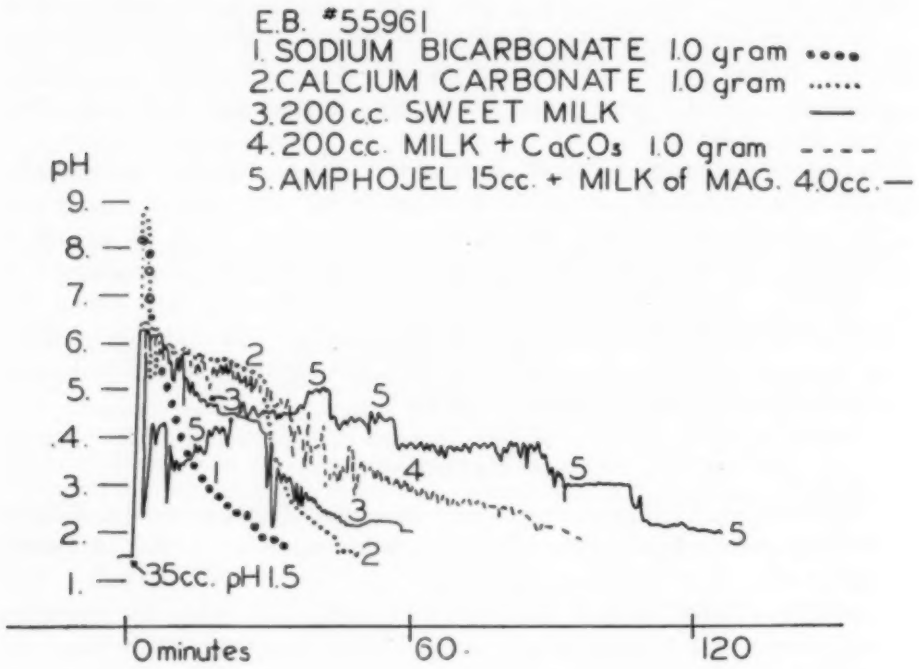

Fig. 1.

as an effective buffer for over two hours without carrying the pH above the upper limits of the physiological range.[1] It is also apparent that 200 c.c. of sweet milk reinforced by the addition of 1 gm. of calcium carbonate, are a more effective buffer than sweet milk, in the same quantity, when used alone.

Discussion

It is apparent from the above tracing that the addition of calcium carbonate to milk enhances the buffering properties of the milk, which, in turn, prevents the calcium carbonate from causing an excessive pH rise.[1] The prolonged effect of the combination would also avoid the often unpleasant necessity of repeated administration of milk alone at frequent intervals.

Similarly, the combination of milk of magnesia and colloidal aluminum hydroxide results in more prolonged effect than colloidal aluminum hydroxide alone,[1] with the subsequent necessity of smaller and less frequent doses. The undesirable initial rise in pH resulting from the use of milk of magnesia alone [1] is avoided, and the constipating effect of aluminum hydroxide is offset. The milk of magnesia content may be varied from 4 to 15 c.c. without raising the pH of the resultant mixture above 7.5, and affords a means of supplying any desired laxative action. This mixture has been used clinically on the Second (Cornell) Medical Division, Bellevue Hospital, with excellent results and will be reported in a later communication.

Summary

1. A simplified method for the continuous recording of gastric pH in the human being is described.

2. Amphoteric substances, such as milk and colloidal aluminum hydroxide, buffer alkalies, such as calcium carbonate and milk of magnesia, in their alkaline range.

3. Calcium carbonate 1 gm. in 200 c.c. of milk, and milk of magnesia 4 c.c., and colloidal aluminum hydroxide 15 c.c. in 200 c.c. of water, are long acting antacids.

4. The buffering effect of these combinations in the human being is readily demonstrated with this method.

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CASE REPORTS

PHEOCHROMOCYTOMA OF THE ADRENAL ASSOCIATED WITH PERSISTENT HYPERTENSION; CASE REPORT *

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For most patients with *persistent*, severe hypertension there is little hope of inducing a complete and uncomplicated cure. The classical syndrome of paroxysmal episodes of severe hypertension associated with pheochromocytoma of the adrenal gland is well known (Howard and Barker [1]). The fact that pheochromocytoma of the adrenal may at times be associated with a persistent, severe hypertension has been described by Kirshbaum and Balkin.[2] However, this fact is not generally appreciated. The present case is reported in view of a striking improvement in blood pressure which was associated with the removal of a pheochromocytoma in a patient who had been followed for several years with a diagnosis of "malignant hypertension."

Case Report

Patient J. M. B., a 40 year old white, married woman, entered the Peter Bent Brigham Hospital for the first time on April 2, 1943, with the chief complaint of headache and known hypertension of approximately seven years' duration. In 1934 she had had her first and only pregnancy which terminated in the birth of a normal, full-term child. During pregnancy, hypertension or signs of toxemia of pregnancy were not observed; systolic blood pressure readings did not exceed 120 to 130 mm. of Hg. In March 1937 during the course of a routine examination a striking elevation of blood pressure (220 mm. Hg systolic and 150 mm. diastolic) was discovered. Subsequent examinations confirmed this finding and the patient was referred to a hospital for more complete study. At that time her chief complaint concerned occasional severe headaches, often associated with nausea, rarely with vomiting. Physical examination revealed a blood pressure of 220 mm. Hg systolic and 120 mm. diastolic, heart of normal size without significant murmurs, and some narrowing of the arteries in the fundus oculi. No hemorrhages or exudates were noted at this time. Laboratory examinations, including urinalysis, kidney concentration tests, phenolsulfonphthalein excretion, blood urea nitrogen, serologic reactions, sedimentation rate, electrocardiogram, roentgenogram of the heart and basal metabolic rate, were not remarkable. Since no etiological factor was disclosed, a diagnosis of idiopathic malignant hypertension was made and a program of restricted activity with sedation was outlined.

In November 1937 because the headaches had become more severe, the patient was seen by another medical consultant who confirmed the earlier findings but in addition noted some blurring of the discs, increased light reflex along the retinal

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vessels and numerous fine white linear scars in both fundi. To complete the study an intravenous pyelogram was advised but was not performed at that time.

In March 1938 her case was again reviewed and no new changes were noted other than a progression of the alterations in the fundi now consisting of marked narrowing of the arteries, wide light streaks, tortuous and engorged veins, marked arteriovenous compression and numerous radial streaks interpreted as old hemorrhages. During the intervening five years (1938–1943) no new symptoms had developed other than increased fatigue on exertion. The headaches were promptly relieved in the prodromal stage by empirin and codeine. The blood pressure was found consistently to be elevated, ranging from 200 mm. Hg systolic and 150 mm. diastolic to 260 mm. systolic and 160 mm. diastolic. No paroxysms of increased hypertension were noted, nor was her blood pressure ever observed to be within normal range. In 1943, before considering the possibility of sympathectomy for the relief of hypertension, intravenous pyelography was performed. This revealed that the left kidney was abnormally low in position with a soft tissue mass above it. A tentative diagnosis of adrenal tumor was made and the patient was referred to this hospital for further diagnosis and recommendation. Inquiry at this time (1943) revealed no history of paroxysmal attacks of palpitation, sweating, tremor, dizziness or weakness. There were no cardiopulmonary complaints other than fatigue and shortness of breath on moderate exertion. The family history revealed that her father had died of coronary occlusion, that two of his siblings suffered from angina pectoris, that her mother had hypertension and that one of the patient's sisters died in infancy of a congenital heart lesion. The past history of the patient revealed that she had always been in good health up to the onset of the present illness.

Physical examination on admission to the Peter Bent Brigham Hospital on April 2, 1943, revealed a well-developed and well-nourished white woman in no acute distress. Weight was 58.6 kg., temperature 98.6° F., pulse rate 80 per min., respirations 20 per minute, and blood pressure 270 mm. Hg systolic and 160 mm. diastolic in both arms. The arteries of the fundus oculi were very narrow with a sharp light streak; the veins were distended and tortuous; there was striking arteriovenous compression and small white lines radiating from the discs with no evidence of recent hemorrhages, exudates or papilledema. The heart was slightly larger than normal. The first heart sound at the apex was accentuated; the aortic second sound was exceedingly loud and ringing; there were no murmurs, and the heart rate was regular. The chest was clear. There were no abdominal striae, and no masses could be felt in the abdomen; external genitalia were normal; pelvic, rectal and neurological examinations were not remarkable. There was no edema of the extremities. The blood pressure in both legs was 250 mm. Hg systolic and 150 mm. diastolic to 270 mm. systolic and 160 mm. diastolic. Hair distribution over the body was of normal female type; there was no acne. Adipose tissue was generally distributed over the body.

Laboratory examination: Blood Hinton and Wassermann reactions were negative. Urinalysis revealed a specific gravity varying from 1.010 to 1.015, a slight trace of albumin with occasional red blood cells, white blood cells, hyaline and granular casts. Red blood cell count was 3.8 million, hemoglobin 12.4 gm., hematocrit 37 per cent volume packed cells, white blood count 5.8 thousand with a normal smear and differential count. Blood chemical studies revealed a blood urea nitrogen of 14 mg., non-protein nitrogen 23 mg., serum protein of 7.3 gm., serum albumin 3.9 gm., serum globulin 3.4 gm., blood sugar 81 mg., and blood cholesterol of 235 mg. per 100 c.c. Serum chloride was 100 m. eq. per liter and carbon-dioxide combining capacity 28.2 m.M. Urine culture was sterile. Phenolsulphonphthalein test revealed 25 per cent of the dye excreted in 15 min. and a total of 50 per cent in two hours. Seventeen-ketosteroid excretion was 6.7 mg. and 7.3 mg. per 24 hours on two occasions (normal for adult females being 8 to 12 mg.). An oral glucose tolerance curve revealed a

fasting-blood sugar level of 130 mg. per 100 c.c.; ½ hour after ingestion of 100 gm. of glucose blood sugar was 100 mg., at 1 hour 68 mg., at 2 hours 77 mg. and at 3 hours 85 mg. Roentgenogram of the heart showed it to be transverse in position, prominent to the left with an elongated, tortuous aorta; on fluoroscopy there was a good regular beat with increased pulsation along the right border; the heart was 5 per cent above

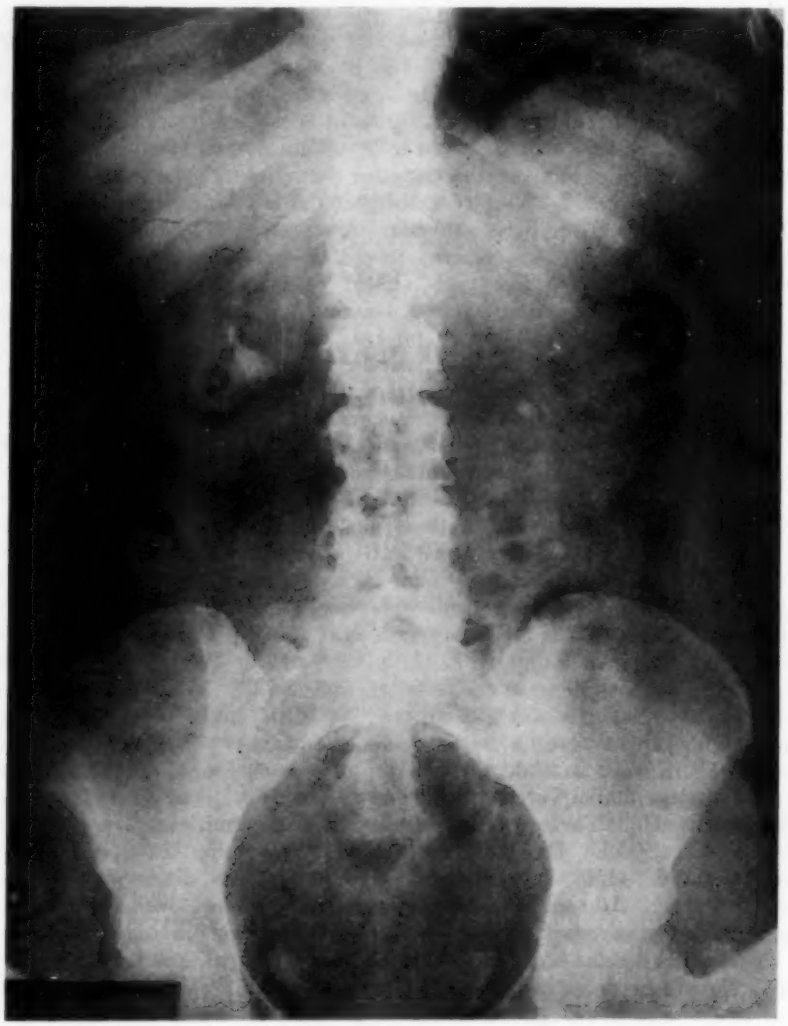

FIG. 1. Tumor of the left adrenal region displacing left kidney downward.

average by height-weight ratio. An electrocardiogram revealed an abnormal form of ventricular complex with T_1 and T_2 diphasic and T_3 inverted, Lead IV being normal. Stereoscopic films of the skull showed a vault of average thickness, with no localized changes or signs of pressure. The pituitary fossa was normal. A sodium amytal blood pressure depression test with the use of 0.4 gm. of the drug in a single dose was followed by a lowering of blood pressure from a level of 240 mm. Hg systolic and 140 mm. diastolic to 180 mm. systolic and 110 mm. diastolic.

Dr. Lewis Dexter attempted to recover epinephrine or epinephrine-like substances from the urine of this patient prior to operation. Employing the method of Richter [8] it was impossible to demonstrate any epinephrine-like activity before operation, or after operation at a time when the patient was receiving sizeable injections of adrenalin in aqueous solution and in oil.

An intravenous pyelogram disclosed prompt excretion following the injection of 20 c.c. of diodrast. It was apparent that the left kidney was much lower than normal in position and somewhat rotated. The excretion of dye was less complete on the left side than on the right. There was a large soft tissue mass visible above the left kidney (figure 1). The upper pole of the left kidney was not delineated to a satisfactory degree. A report on cystoscopic examination follows:

"The cystoscope was introduced with ease. The bladder wall was normal. No. 5 whistle-tipped catheters were passed up either ureter a distance of 28 or 29 cm. on the right, but on the left to only 25 cm. beyond which it would not pass, apparently this kidney being low. There was a good flow of urine from both sides. Microscopic inspection of both ureteral and bladder urines was negative except for a few red cells

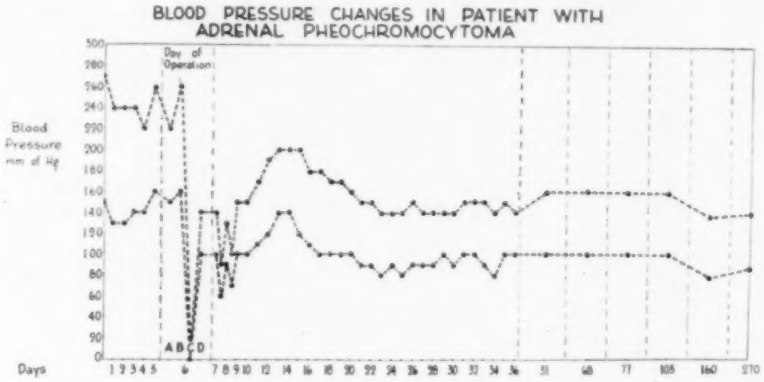

CHART 1.

on the right, apparently traumatic in origin. Cultures were taken from both ureteral urines and from the bladder urine, and divided function tests with PSP were made. This showed an appearance time of 3 minutes on the left and 3½ minutes on the right. The 10-minute volume was 8 c.c. on the right and 23 c.c. on the left. Dye excreted on the right in 10 minutes was 3.5 per cent; on the left, 5.5 per cent."

From these examinations it appeared probable that this patient was suffering from a tumor arising in the upper pole of the left kidney or adrenal region. In the absence of virilism, diabetes, osteoporosis, acne, abdominal striae and with a normal level of 17-ketosteroid excretion, a hyperfunctioning tumor of the adrenal cortex did not seem likely. The differential diagnosis thus was limited to:

(*a*) A tumor of the left kidney or adrenal coincidentally associated with hypertension or

(*b*) A tumor of the adrenal medulla (pheochromocytoma) responsible for *persistent* hypertension.

With the possibility of this latter diagnosis well in mind, the patient was transferred to surgery and precautions were taken to provide for the treatment of either acute adrenal cortical deficiency or acute medullary deficiency or both during and following operation.

Operation: (Dr. William C. Quinby) "Under ether anesthesia the region of the kidney was exposed through a transverse subcostal incision on the left. The kidney was found to be low, easily mobilized and of normal size. Above the left kidney the tumor was visible and palpable, attached to the upper pole. The superior and larger portion of the tumor had a well-developed capsule and was not adherent to the surrounding fat; the lower portion of the tumor was fixed to the kidney by adhesions of delicate character. Further dissection found that the blood supply of the tumor entered it at several points; the principal blood vessels, however, came from the renal pedicle. Toward the end of the operation, as the tumor was being mobilized and while the blood vessels were being severed one at a time, the patient's blood pressure began to fall, at first slowly and then precipitously until neither pulse nor blood pressure could be obtained—although 5 minutes previously blood pressure had been

TABLE I

Summary of Specific Hormone Therapy for Collapse Which Followed Removal of Adrenal Tumor *

Period	Adrenalin 1 : 1000	Adrenalin-in-Oil	Eschatin	Percorten	Other Medication
Acute collapse during operation	2 c.c. I.V. 2 c.c. S.C.	3 c.c. I.M.	30 c.c. I.V.		Transfusion whole blood. Glucose and saline solution I.V.
First day following operation	0.5 c.c I.V. 3.0 c.c. I.M.	2 c.c. I.M.	20 c.c. I.V. 30 c.c. S.C.	10 mg. I.M.	I.V. plasma. Glucose and saline solution.
Second day following operation	0.5 c.c. I.V. 1.0 c.c. S.C.		20 c.c. I.V. 20 c.c. I.M.	10 mg. I.M.	
Third day following operation			20 c.c. I.M.		

*I.V. = intravenous administration
S.C. = subcutaneous administration
I.M. = intramuscular administration

recorded as 240/160 mm. Hg. (See chart 1.) One c.c. of adrenalin was injected in the antecubital vein, 1.0 c.c. in the renal vein, and 2.0 c.c. subcutaneously; 3.0 c.c. of epinephrine-in-oil were injected intramuscularly; a transfusion of whole blood was begun and 30 c.c. of adrenal cortex extract were given together with the transfusion, since the size and state of the right adrenal was not known. Following this, systolic blood pressure was restored to a level of 150 to 170 mm. Hg. The tumor was completely removed, there being no evidence of involvement of regional lymph nodes or extension of tumor into any of the surrounding structures. At the close of the operation the patient's condition was entirely satisfactory, her blood pressure being 140/100 mm. Hg."

Postoperative period: The first 24-hour period following removal of the tumor was characterized by periodic episodes of hypotension (systolic pressure of 70 to 90 mm. Hg) which responded to epinephrine therapy, intravenous plasma and saline

solution, and for which relatively large doses of adrenal cortex extract were given, since the possibility of adrenal cortical insufficiency could not be eliminated. Between these periodic episodes of hypotension the systolic blood pressure was maintained at a level of 110 to 140 mm. Hg. Specific therapy during the operation and for the three days following operation is summarized in table 1.

FIG. 2. Pheochromocytoma of the left adrenal (size: 9.3 cm. by 7 cm. by 6 cm.).

During the second, third and fourth days following operation the systolic blood pressure slowly stabilized between 130 and 140 mm. Hg, and the episodes of hypotension became less frequent and less marked (chart 1). Adrenalin and adrenal cortex extract therapy were gradually reduced during this period and were discontinued altogether on the fourth postoperative day (table 1). On the fourth and fifth days following operation the patient's temperature was elevated and atelectasis of the right lower lobe of the lung was noted. This subsequently cleared, and with the exception of a slight infection of the wound, the patient made an uneventful recovery. She

was discharged from the hospital four weeks following operation, at which time her blood pressure (resting in bed) was 130 mm. Hg systolic and 80 mm. diastolic. Subsequent examinations (chart 1) reveal that her blood pressure has continued to remain at this level. When up and about and when examined after a rest period blood pressure readings averaged 160 mm. Hg systolic and 100 mm. diastolic.

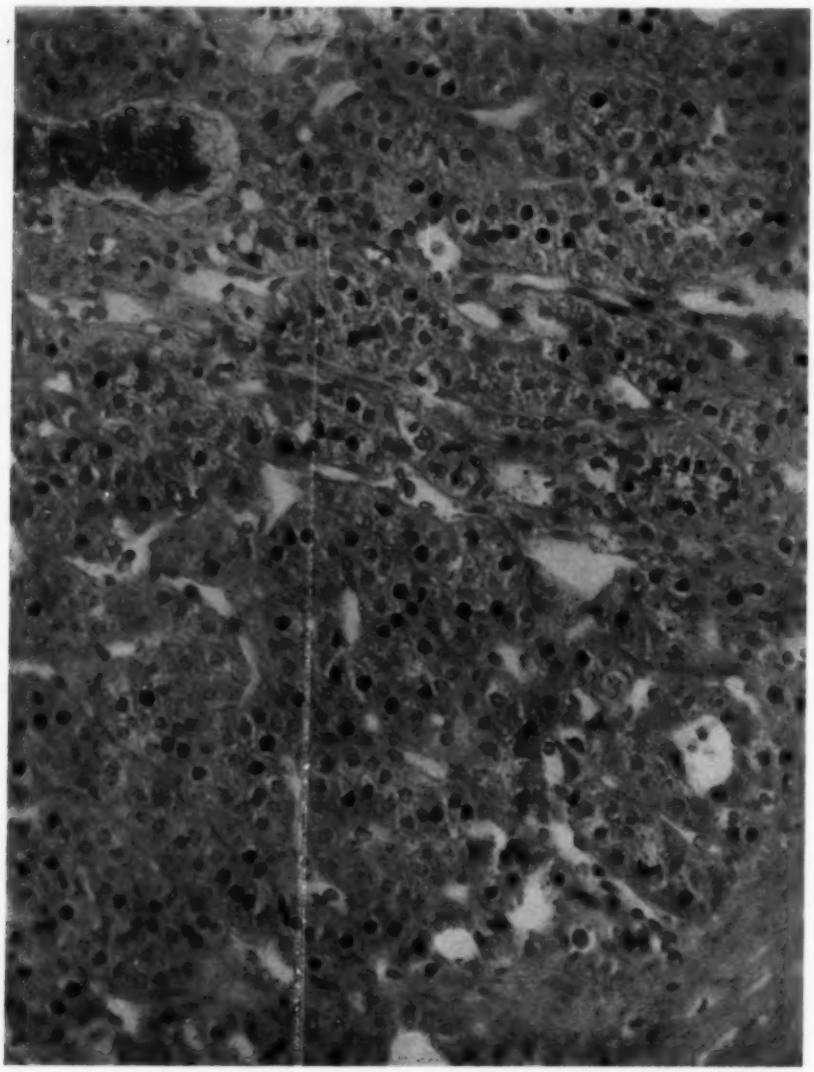

FIG. 3. Photomicrograph of adrenal pheochromocytoma. Magnification: 300 ×.

Retinal examination revealed a progressive disappearance of the high-grade changes in the fundi which were noted upon admission. On the day following operation a few fresh hemorrhages were noted; since that time no new hemorrhages have been observed. There has been a gradual increase in the size of retinal arteries until at present they approach the normal in caliber and appearance.

Pathological report: (Dr. Clinton V. Z. Hawn). The tumor measured 9.3 cm. by 7 cm. by 6 cm. and weighed 220 gm. (figure 2). The tumor mass appeared to be well encapsulated and at one pole adrenal tissue appeared to be embedded. The cut surface was deep purple in color and apparently congested with a considerable amount of blood. Histologically the tumor tissue varied greatly from area to area. Characteristically the tumor cells were arranged in rounded masses which were separated by fine strands of connective tissue among which were numerous endothelial lined spaces (figure 3.). The individual cells were large, polyhedral or elongated which on Schmorl's staining showed fine granules of an olive green color revealing their chromaffin nature. In many areas the tumor had undergone degeneration. In some areas there had been extensive invasion of the capsule by the tumor masses and in some places extracapsular extension.

Analysis of tumor for epinephrine content: Through the courtesy of Dr. D. K. Kitchen of Parke, Davis and Company, a specimen of this tumor was analyzed for its epinephrine content. The tumor had been kept frozen since its removal, but unfortunately was not iced when forwarded to Detroit, Michigan, during the early summer. Therefore, the analyses of epinephrine probably represent only a fraction of the concentration which was originally present in the tumor.

"The extract of wet gland, representing a yield of 60 c.c. from 27 gm. of tissue (total tumor weight = 220 gm.) has been tested for adrenalin content and each c.c. found to be equivalent to 0.275 mg. of standard adrenalin. The action of the extract was definite, and characteristic of adrenalin activity."

Subsequent course: Because of the nature of the histological changes, it was felt advisable to irradiate the region of the left kidney. Hence 27 roentgen-ray treatments, with a total dose of 5400 roentgen units, were administered. At present, the patient feels well, is able to carry on her own work at home; headaches have disappeared, and when last seen 270 days following operation she appeared to be in very good physical condition. Her blood pressure (resting in bed) is 140 mm. Hg systolic and 88 mm. diastolic.

Discussion

Surgical removal of adrenal tumors is likely to induce acute epinephrine or adrenal cortical deficiency depending, of course, upon the type of tumor. For patients with adrenal cortical tumor, without excessive hypertension, it is our custom to use adrenal cortical hormone therapy, prior to, during and following operation. The preparations and dosages which we use are similar to those employed in the treatment of acute adrenal crises.[4] In the case of a patient with excessive hypertension one hesitates to administer either adrenal cortical or adrenal medullary preparations preoperatively. For this reason, quick action is required when blood pressure begins to fall during the removal of the tumor. An immediate precipitous reduction in blood pressure at or about the time the tumor is removed suggests acute adrenal medullary deficiency rather than adrenal cortical deficiency. In treating the hypotension of patient J. M. B. we administered quantities of adrenal cortical extract large enough to correct adrenal cortical deficiency and then were relatively safe in assuming that a sudden drop in blood pressure during the postoperative period represented epinephrine deficiency and could be corrected by the prompt administration of this hormone. The use of adrenalin-in-oil, intramuscularly, was of great aid in providing for a more sustained rise in blood pressure.

Summary

The possibility of hypertension associated with pheochromocytoma of the adrenal must be considered in the differential diagnosis of patients with so-called "malignant hypertension."

Vascular changes resulting from long-standing hypertension may be reversed following restoration of blood pressure to a more nearly normal level.

Removal of an adrenal pheochromocytoma always presents the possibility of collapse from acute epinephrine deficiency as well as the possibility of inducing adrenal cortical insufficiency. Both may require immediate and heroic therapeutic measures.

Conclusion

Pheochromocytoma of the adrenal must be thought of as a possible cause of persistent, severe hypertension. This is one form of severe hypertension which may be readily amenable to surgery. The occurrence of acute epinephrine deficiency during ligation of the veins leading from the tumor requires prompt therapy.

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A CASE OF TRANSIENT SUCCESSIVE PULMONARY INFILTRATION (LOEFFLER'S SYNDROME) ASSOCIATED WITH TRICHINIASIS *

By James F. Slowey, M.D., *Cleveland, Ohio*

In 1932 William Loeffler,[1] professor of medicine at the University of Zurich, described the syndrome that bears his name. Subsequently, in 1934, he reported 12 additional cases at the Fourth International Radiological Congress in Zurich and additional ones in 1936, a total of 51 cases.

The salient features of the syndrome are transient, successive pulmonary infiltrations with eosinophilia. The pulmonary manifestations are variable, large or small areas of the lung being involved. It may be unilateral, bilateral, homogeneous or nodular. It may disappear in one area and become manifest in an-

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other, the lesion being transient in character. The particular area involved usually clears within two weeks.

The patients are not severely ill, and the condition is often discovered in the course of a routine examination. The eosinophilia usually is at its height while the lung is clearing and may vary greatly in degree. Most of the cases reported have come from Switzerland,[2] occurring usually in the spring and summer. Two-thirds of the cases occurred in males. The syndrome has been attributed to various causative agents.

Loeffler was of the opinion that many of the cases were of tuberculous origin. Breton [5] says it occurs in 5 to 8 per cent of asthmatics, and Engel [4] had two cases of possible sensitivity to ligustrum, which flowers in May and June. *Ascaris lumbricoides* was found in two cases by Wild.[2c] It was thought that the larvae penetrated the intestinal wall and were carried by the portal vein or the thoracic duct to the right heart, thence to the lung where they caused a local reaction with atelectasis and penetrated the alveoli and then were coughed or carried up and expectorated or swallowed. Another case is reported by F. Parkes Weber.[7] The patient, a 10 year old boy, had transient pulmonary infiltration with eosinophilia, and had previously passed *Ascaris lumbricoides.*

In most instances the condition is thought to be of an allergic nature. Kline and Young [6 a, b, c] have described a condition of the lungs due to a reversible allergic reaction in the bronchi and interstitial tissues in cases of bronchial asthma that could very well explain many cases of Loeffler's syndrome even though the causes of the allergy might be different, e.g., pollen, *Ascaris lumbricoides,* or some other agent.

In postmortem examination of the lungs in cases of bronchial asthma, they found dark red, meaty lungs which contained air. The bronchioles were prominent and thick, and the bronchi and bronchioles contained abundant tenacious greenish-yellow or grayish, viscid material. Microscopically, the lumina of the bronchi were filled with mucus in which there were numerous neutrophilic polymorphonuclears, eosinophiles, and mononuclear cells, some areas of bronchopneumonia, and other areas of hemorrhage. Whereas many of the patients with Loeffler's syndrome are not asthmatic, many of them give a history suggestive of allergy; and the above described type of pulmonary involvement, or some modification of it, is presumably the condition which is present in many of these cases. Because the patients are not critically ill and do not die from the illness, no autopsy material is available.

I wish to report a case of transient, successive, pulmonary infiltration, which was associated with *Trichinella spiralis.*

Case Report

The patient was a rather obese, 47 year old female of Italian descent, and the mother of four children. She was admitted to St. Alexis Hospital, Cleveland, on November 3, 1940.

Three weeks previous to admission, she was treated at home for sore throat and acute coryza. At that time, she had no cough or pains in her chest. About 11 days before admission she began to complain of left upper lumbar backache and chest pains.

At this time, she had an occasional mild cough and slight elevation of temperature. She was treated with sulfanilamide by her family physician but did not improve.*

Hospital Course. On admission, she was cyanotic and in respiratory distress. Perspiration was profuse. Her temperature was 103° F., with pulse rate of 108. The respiratory rate was 28, and the blood pressure reading 90 mm. Hg systolic and 60 mm. diastolic. Her throat was slightly injected. The heart was normal, and there was a slight dullness in the left base with fine râles in this area.

The laboratory examinations revealed the following. Estimation of the blood sulfanilamide 5.5 mg. per cent. White blood cells 22,000; red blood cells 4,810,000; hemoglobin 13 gm.; sedimentation rate, 120. Differential count: Polymorphonuclears, 67; small lymphocytes, 2; large lymphocytes, 3; eosinophiles, 23; monocytes, 4; basophiles, 1. Blood platelets, normal.

Sputum examination showed gram positive streptococci and gram positive diplococci and staphylococci. No Quellung observed with specific pneumococcic typing sera. The roentgenogram of the lungs showed the right lung to be clear, and on the left, "There is increased density over the base of the lung sufficient to obliterate lung detail, but the outline of the heart and the diaphragm are still visible."

The patient was given sulfapyridine, but this was discontinued after five days because of a definite decrease in the number of red blood cells. On the sixth hospital day the temperature was 99° F., and the lungs were clear on physical examination.

The following day numerous coarse râles developed in the right base and the temperature rose to 101° F. On the eighth hospital day, the patient developed a maculopapular pruritic rash on the face, chest and back, the voice became hoarse, and the temperature rose to 102° F. The chest findings remained the same. With no specific therapy, the rash disappeared and the temperature gradually decreased over a period of nine days.

On the tenth and thirteenth hospital days the stools were negative for ova and parasites.

The roentgenographic examination on the fifteenth hospital day showed a band-like area of density in the opposite lung, the left chest being clear.

The patient developed tenderness over the gall-bladder, and the liver increased in size, so that by December 9, her seventeenth hospital day, it was nearly down to the umbilicus. There was no jaundice, the icteric index being 4. The gastric analysis was normal. At this time her feet were slightly edematous.

By the twenty-first hospital day the liver receded to practically normal size, the temperature had dropped to normal, and both lungs were clear. The patient was discharged on December 18, her twenty-sixth hospital day, with a normal temperature. However, she still complained of muscular pains in the arms and legs and would sweat profusely on exertion.

The differential blood counts and sedimentation rates were as follows:

Hosp. Day	Date	W.B.C.	R.B.C.	Hgb.	Eos.	Sed. Rate
Adm. 1	11–23–40	22,000	4,810,000	13 gm.	23%	120
3	11–25–40				16%	
5	11–27–40		4,600,000			
7	11–29–40		3,240,000			
12	12– 4–40				8%	85
14	12– 6–40	11,000	4,600,000	13 gm.	10%	95
	1–21–41		3,730,000		34%	
	4– 8–41	8,900			13%	

* This patient was referred to me through the kindness of J. N. Rini, M.D., the family physician.

Hosp. Day	Date	T. (rectal)	P.	R.	Rash	Sputum	Cough	Cyanosis	Lungs	Liver	Stool
1	11–23–40	103.4°	108	28		Strep. gram pos.; diplococci gram pos.; no pneumococci; bacilli; no acid fast B.	Mild	Marked	Right, clear; left density; left base râles; x-ray confirmation		
3	11–25–40	101.4°	112	32							
6	11–28–40	99°	100	28				Still present	Clear		
7	11–29–40	101°	108	24					Coarse râles; right base		
8	11–30–40	102°	120	32	+				Coarse râles; right base		
10	12– 2–40	101.4°	96	32							Neg. for ova and parasites
13	12– 5–40	101.2°	112	24							Neg.
15	12– 7–40	101°	120	26					X-ray: density right base; left lung, clear		
17	12– 9–40	99.8°	100	24						Large	
20	12–12–40	100.2°	94	24		Strep. gram pos.; diplococci gram pos.; no pneumococci; bacilli; no acid fast B.					
21	12–13–40	99°	92	24					Both lungs, clear		
	1–21–41							Slight	Both lungs, clear	Normal	

At home, the patient gradually improved. The muscle pains decreased and the sweating became less.

She was prevailed upon to have a muscle biopsy, which was done on April 15. Approximately 100 larvae of *Trichinella spiralis* per 1 gm. of deltoid muscle were found, a number sufficiently large to cause clinical symptoms.

Discussion

This patient at no time had early signs of *Trichinella spiralis* infestation such as puffy eyelids or swelling of the face. There were at no time attacks of diarrhea or epigastric distress, which are usually found with trichiniasis. She did not like ham and was not in the habit of eating it, with the exception that occasionally she ate a little spiced ham in a sandwich.

On admission she had a pulmonary lesion on the left that had been present probably less than 11 days and that cleared six days after admission to the hospital. She then developed consolidation on the other side that cleared in nine days. An eosinophilia was present throughout her illness. At no time was the condition of the patient critical.

I feel that the transient successive pulmonary infiltrations with eosinophilia found in this case were due to an allergic reaction of a reversible type in the bronchi and interstitial tissue of the lungs. Such a reaction could be due either to blood-borne *Trichinella spiralis* antigen causing the local pulmonary reactions or to antigen from trichinella present in the local area of the lung. There is valid immunological evidence that the same type of local reaction could be produced in either event.

The incidence of *Trichinella spiralis* infestation in this country is estimated as being about 20 per cent,[8] varying in different parts of the country. This figure is arrived at by estimation from reports on autopsy findings using both the direct microscopic examination of compressed muscle from the diaphragm, or the diaphragm and some other muscle, and by the Baerman digestive method. A great many of the cases are of the subclinical type, having less than 100 larvae per gram of muscle. In areas where the pigs and hogs are fed on garbage the incidence is higher. Beaver, bear, rats and other animals may be infected.

In spite of the fact that the meat undergoes inspection, many people become infected with *Trichinella spiralis* because of eating infected pork that has not been sufficiently cooked.

Besides the cases reported in this country, there have been cases reported from practically everywhere in the world including Switzerland,[9] whence most of the cases of Loeffler's syndrome have been reported.

In reviewing the literature, there is a relationship between pulmonary disease of Loeffler's syndrome type and trichiniasis. The last case in the series of six reported by C. Maier [9a] was a case with transient pulmonary infiltrations which were accompanied by eosinophilia, but in which trichinae could not be found on muscle biopsy, and it was consequently considered to be a case of Loeffler's syndrome. This may have been a case of trichiniasis with a low grade infestation, the trichinae being so few in number that none was in the specimen of muscle examined.

Several other cases of trichiniasis have been reported having pulmonary symptoms or signs.[10] However, in most of these cases, the pulmonary involvement was slight and was not a prominent feature of the infestation. The first case of trichiniasis reported in detail in the group presented by Minot and Backman had transient pulmonary infiltrations of short duration, and if the trichinae had not been looked for or found, could easily have been considered a case of Loeffler's syndrome of unknown etiology.

Conclusions

1. A case is presented with the findings of Loeffler's syndrome associated with *Trichinella spiralis* infection.
2. Similar cases taken from the literature are cited.
3. Trichiniasis is found occasionally in Switzerland.
4. The majority of the cases of Loeffler's syndrome are reported from Switzerland.
5. Cases of Loeffler's syndrome should have skin tests for trichiniasis and should have ample biopsy sections of muscle examined by the slide compression method for *Trichinella spiralis*.

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A CASE OF NITROBENZENE POISONING*

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NITROBENZENE, or Oil of Mirbane as it is known commercially, is a common solvent for a number of every day substances such as shoe polishes and dyes, lac-

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quers, indelible inks, cheap perfumes, and a variety of other things. It is toxic to man by ingestion, direct contact, or inhalation or a combination of any of these avenues. Sollmann [15] states that a dose of as little as one gram may be fatal. The symptoms and signs of poisoning are nausea, vomiting, prostration, intense gray blue cyanosis, convulsions, and coma (Sollmann). As with other benzene derivatives, there is a direct toxic effect on the blood with rapid and intensive destruction followed in cases of recovery by active regeneration.

In view of the widespread use of substances containing this agent, cases of poisoning are probably more common than is generally believed. However, most of these cases are evidently mild and are probably diagnosed as acute indigestion or other functional upset. Recovery in these cases is rapid with symptomatic therapy. A moderate number of cases of more severe poisonings, either accidental or suicidal, have been reported in the literature. In most of these, the nitrobenzene has been taken orally. Spinner [16] reported 16 cases in women by whom the drug was used orally as an abortifacient in doses of 15 to 100 grams. Seven patients died and in only one case did an abortion result. He noted that recoveries had occurred after doses as large as 400 grams. Other authors [2, 4, 12, 13, 18, 19, 20] report recoveries from doses ranging from 3 to 100 grams. On the other hand, Muller [9] noted a case in which death followed ingestion of 25 c.c. of nitrobenzene, and Smith [14] reported a case which died following ingestion of 90 c.c. of marker ink containing nitrobenzene or aniline. Fullerton [8] cites one suicide from nitrobenzene, and the Office of the Chief Medical Examiner of New York City [11] records five deaths from ingestion of nitrobenzene in the four years from 1936 to 1939, inclusive. Of these, four evidently drank shoe polish or dye, and the fifth used a cleaning fluid containing nitrobenzene.

The largest number of cases of poisoning by contact was noted by Stifel [17] who reported 17 cases of severe cyanosis, headache, malaise, and vertigo following the wearing of freshly dyed shoes. The dye contained nitrobenzene and the etiology of the syndrome was confirmed by experiments on animals and men. Recovery in all cases was prompt. Erskine [7] noted four sisters who became ill following the use of a furniture polish containing nitrobenzene. Clark and Paul [3] report a case of poisoning occurring after the nitrobenzene was spilled on some wearing apparel. Poisoning in some of the contact cases was probably partially due to inhalation of the nitrobenzene which is moderately volatile. Dresbach and Chandler [5] showed that the effects of nitrobenzene fumigation on animals were largely nervous. There was an initial stimulation and then a paralysis of the motor centers of the skeletal muscles with little effect on circulation or respiration.

The authors had occasion to follow one case of nitrobenzene poisoning with recovery. The case is presented here.

Case Report

M. M., a 30 year old white man, while on a drinking bout, ingested 15 c.c. of black laundry marker ink mixed with 15 c.c. of denatured alcohol. He remembered nothing after this and was brought into the hospital 11 hours later. Past history, family history, and social history were essentially negative except for a post-parotitic orchitis.

Physical examination revealed a well developed, thin, acutely ill, anxious and agitated white male with rapid, irregular, rattling respiration. There was a marked

generalized gray blue cyanosis with slate blue color of lips, nails, and tips of ears. The skin, particularly that of the forehead, was covered with a cold perspiration. The teeth, mucous membranes, and tongue were stained with dark blue material. The lungs were clear. The heart was normal in size, and the sounds were clear. The first sound was split at the apex but there were no murmurs. Pulses were rapid, thready, slightly irregular, and the rate was 140. The remainder of the examination including the neurological was essentially negative except for an atrophic right testis.

Laboratory findings on admission. Blood count: White cells 28,100; hemoglobin 85 per cent; red count 4.39 million; polymorphonuclears 73 per cent; lymphocytes 27 per cent; platelets 260,230. Two urine specimens showed a slight trace of albumin. Blood chemistry: Sugar 137 mg. per cent, non-protein nitrogen 32 mg. per cent, CO_2 combining power 15.5 volumes per cent. Bleeding time was one and one-half minutes and clotting time three minutes. Fragility test showed hemolysis at .35 to .25 per cent saline. Serologic reactions were negative. Blood and urine were positive for anilin.

Hospital course and treatment. On admission, the patient was given caffeine subcutaneously followed by lavage with sodium bicarbonate solution. A continuous intravenous drip of 5 per cent glucose in normal saline was given. Oxygen and CO_2 inhalations were also given because of the character of the respirations and the cyanosis. The patient improved gradually. His color returned to normal on the fourth hospital day, and the pulse and respiration reached normal levels on the third hospital day. There was a spiking temperature until the third day, followed by a slight elevation until the sixth day after which normal levels were maintained. The patient's further convalescence was uneventful except for an acute exacerbation of a chronic otitis media with a small amount of discharge. This responded readily to routine therapy. The patient was discharged in good condition on the fourteenth hospital day.

Laboratory findings while in the hospital. The CO_2 combining power returned to normal in one day. The white cell count dropped to between 7,000 and 12,000 on the second hospital day. On the sixth hospital day the differential count showed polymorphonuclears 29, lymphocytes 66, monocytes 2, eosinophiles 2, basophiles 1; and two days later (eighth hospital day) polymorphonuclears 63, lymphocytes 30, monocytes 6, eosinophiles 1. Subsequent counts were essentially the same. A glucose tolerance test was normal. Blood cholesterol was 175 mg. per cent, and cholesterol esters 64 mg. per cent. Blood total proteins on three occasions varied from 4.5 to 5.5 per cent with a definite increase in the A/G ratio. Bromsulfalein liver function test showed 5 per cent retention in one-half hour. On admission the blood was dark brown in color and clotted very quickly. No examination for methemoglobin could be done at the time of admission but anilin was present for several days. One week later there was no methemoglobin present on spectroscopic examination. An electrocardiogram and urine concentration test done during the hospital stay were normal.

Comment

This case is of interest from several points of view. The ingestion of laundry marker or indelible ink is relatively uncommon. Smith [14] in his case report notes that the substance used was marking ink which contained anilin and probably nitrobenzene. His patient showed the classical picture of nitrobenzene poisoning with marked cyanosis, stertorous respiration, coma, and twitching of hands and feet. Death occurred 12 hours after ingestion. The manufacturers of the ink used in the case presented here reported that they knew of no other individuals who had taken their ink internally.[10]

The effect of the nitrobenzene on various organ systems is well illustrated in

this case. The most prominently involved was the circulatory system. Initially there was a marked cyanosis due largely to formation of methemoglobin, although this substance was not demonstrated because of lack of facilities. There were later changes in the differential cell count due to the direct toxic action of the poison. These were transitory and there was no appreciable effect on the red corpuscles. The hemodynamic changes were probably a result of the direct toxic effect of the nitrobenzene on the heart as well as of the anoxemia consequent to the low utilizable hemoglobin. They were manifested by signs of shock and a rapid, thready pulse. The rapid coagulation time and the color of the blood initially are findings which are difficult to explain. Similar findings were noted by other observers.[7, 9, 12, 20]

The respiratory system was also involved. The respiratory changes were probably the result of a direct toxic effect of the nitrobenzene on the respiratory center combined with the indirect effect resulting from the cerebral anoxemia associated with the massive formation of methemoglobin. The forced rapid respiration noted here accounts in large part for the low CO_2 combining power obtained on the first day. In addition, there was an evident disturbance in acid base balance due possibly to toxic or dehydration changes.

The changes in the respiratory and circulatory systems were rather marked in contradistinction to the findings of Dresbach and Chandler[5] who note that respiratory and circulatory changes are minor. In their experiments, the major reactions were in the nervous system. Although this case does not show any outstanding nervous manifestation, other authors[3, 4, 14, 16, 17, 19, 20] have noted many nervous disturbances including paralysis, coma, involuntary movements, twitching, headache, vertigo, and irritability. Many of these symptoms and signs may have been due to cerebral anoxemia rather than a direct toxic effect.

The gastrointestinal tract was not noticeably upset in this particular case, although the fact that the patient was not seen immediately may account for the absence of gastrointestinal signs. Gastrointestinal symptoms and signs in nitrobenzene poisoning have been noted frequently in other cases[3, 9, 17, 19] and consist of nausea, vomiting, and abdominal discomfort. They are probably due in part to direct irritation and in part to central nervous system changes.

The liver was evidently definitely involved by the poison, although the denatured alcohol ingested may have contributed in some part to the changes in the liver despite the small amount of this substance taken. There were several findings which indicated decreased liver function. The low total protein with increased A/G ratio pointed to change in the liver which organ largely regulates the globulin fraction of the blood. In addition, there was a decrease in cholesterol esters also indicating liver damage, and last, the bromsulfalein test showed slight but significant retention. It is also possible that the decreased coagulation time and the increased viscosity of the blood may have been due partially to changes in the liver. Wright-Smith[19] noted changes in the urine which might have been attributable to liver damage (bile pigments).

Other organs and systems were not appreciably involved clinically. The pathological changes in the organs involved could not be determined in this case, but there have been various findings in autopsied cases and experimental animals dying from nitrobenzene poisoning.

The most common finding at autopsy was marked cyanosis of the skin and

viscera. The majority of cases showed considerable congestion of all organs, particularly the lungs, with occasional edema of the brain. In one case [9] there were multiple small hemorrhages in the heart, lungs, liver, kidneys, brain, and stomach, and in others there were erosions of the esophagus [14] and ecchymoses in the stomach.[8] Dresbach and Chandler [6] noted chromatolysis of Purkinje cells in animals poisoned with nitrobenzene. In the five cases from the Office of the Chief Medical Examiner of New York City [11] nitrobenzene was found chemically in all cases in either stomach, liver, brain, or blood. It was in the liver in four cases, the highest concentration being 62 mg. per 500 grams of liver. The concentration of nitrobenzene in the brain in the two cases in which the brain contained the substance was 82 mg. per 500 grams.

Treatment of nitrobenzene poisoning, like that of other poisons, consists generally of attempting to remove the poison or to hasten its excretion while at the same time using general supportive measures. In this case stimulation and lavage were used at first followed by intravenous glucose in normal saline and CO_2 and O_2 inhalations. The glucose was used to fortify the liver, the saline to replace that lost by vomiting and lavage and to aid in restoring the acid base balance. CO_2 and O_2 were given to stimulate respiration and also to attempt to decrease the cyanosis. Exsanguination followed by transfusion was considered but improvement was so rapid that it was not performed.

As a rule, the same general routine was followed in the treatment of the cases reported in the literature. The most important toxic effect of the nitrobenzene is in the formation of methemoglobin. Therefore, the reduction in the amount of methemoglobin formed and the prevention of its formation are highly desirable end results. Oxygen inhalation, the higher the concentration the better, is of value for these purposes; Brooks [1] has shown that intravenous glucose is effective not only in preventing methemoglobin formation but also in reducing methemoglobin already formed to hemoglobin which can then form oxyhemoglobin. Obviously, then, these two agents come as close to being specifics for the treatment of nitrobenzene poisoning as any known at present. Walterskirchen [18] cites one case of nitrobenzene poisoning treated with methylene blue intravenously. The patient recovered, but glucose was also used so that the exact value of the methylene blue cannot be determined. Pruett and Baum [12] noted the decreased coagulation time and the increased viscosity of the blood in their case and treated it with the usual method but in addition giving ex-sanguino transfusion followed by 500 c.c. of 4.5 per cent sodium citrate solution intravenously, the latter being used to reduce viscosity and increase coagulation time. In very severe cases of poisoning, the value of ex-sanguino transfusion is unquestionable, removing as it does the methemoglobin and the nitrobenzene and replacing these with utilizable hemoglobin. Stimulation and other supportive measures are always to be used as indicated by the individual case.

The recovery of this patient despite the relatively large and frequently fatal dose of nitrobenzene ingested is significant because it may possibly indicate the efficiency of the particular type of treatment used. However, as noted above, recoveries have occurred with much larger doses than this one when no specific routine of therapy was followed. Hence, it would seem that there is a large individual factor determining susceptibility to nitrobenzene and recovery from poisoning with this agent.

Conclusions

Because of the wide range of use of substances containing nitrobenzene, poisoning with this agent is probably more common than is generally believed, although most cases are mild.

Nitrobenzene affects mainly the circulatory, respiratory, and central nervous systems both directly by toxic action and indirectly by formation of methemoglobin with resultant anoxemia. It also affects the liver and hematopoietic system causing damage by direct toxic action.

In the fatal cases, the major autopsy findings were marked cyanosis, marked congestion, and in a moderate number, multiple subserous hemorrhages. The nitrobenzene was found in liver, brain, stomach (washings usually), and blood.

The best treatment for nitrobenzene poisoning after the initial lavage is oxygen inhalation and intravenous glucose supplemented by stimulants, supportive measures, and ex-sanguino transfusions when indicated.

Summary

1. A number of cases of nitrobenzene poisoning from the literature are reviewed briefly.

2. A case of nitrobenzene poisoning is presented. The agent containing the nitrobenzene was laundry marker ink.

3. The case presented here and those in the literature are discussed from the viewpoints of clinical manifestations, pathological changes, and treatment.

4. A number of conclusions concerning nitrobenzene poisoning are made.

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LONGEVITY IN VENTRICULAR ANEURYSM; REPORT OF A CASE FOLLOWED OVER A TEN YEAR PERIOD *

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Although ventricular aneurysm may be compatible with good health and even with strenuous physical activity over a short period of time, it is most unusual that an individual with a progressively enlarging aneurysm of the left ventricle is able to continue his daily activity and maintain himself as a useful, productive member of society for a period of 10 years before succumbing to his underlying cardiac disease. The following case is reported because of the degree of well-being achieved over this number of years during which time the patient was closely followed clinically, radiographically and electrocardiographically.

Case Report

P. E., a 48 year old Russian-born machine operator in the cloak and suit industry, on September 24, 1931 developed severe epigastric pain radiating into both arms and a sense of tightness in the chest which lasted for 12 hours. A diagnosis of cardiac infarction was made. Morphine was administered and hospitalization was advised.

Mild glycosuria had been discovered 10 years previously, but on dietary restriction alone there had been no recurrence. There was no history of hypertension. He had been in good health until four months prior to this time when on exertion he developed episodes of pain in the epigastrium, chest and in both upper extremities, dyspnea and nausea. Medication afforded but temporary relief, and the attacks soon became more frequent and severe in character, never, however, so severe or prolonged as that on September 24, 1931.

When first seen he presented a picture of shock. The heart was not enlarged to percussion; the first apical sound was faint; a pericardial friction rub was present. The white blood cell count was 18,000 with 89 per cent polymorphonuclear leukocytes. A transient glycosuria was noted. The electrocardiogram was that of anterior wall infarction (figure 1 a).

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From the Medical Service of the Montefiore Hospital, New York, N. Y.
The opinions and views set forth in this article are those of the authors, and are not to be construed as reflecting those of the United States Army or of the Navy Department.

The temperature rose to 101.6° F. the following day and remained slightly elevated for the subsequent month. The pericardial friction rub was more distinct on the second day but thereafter was no longer audible. On the fourth day there occurred a pulmonary infarction of the right lower lobe which was followed by a pleural effusion on the same side. His blood pressure fell from the initial 130 mm. Hg systolic and 80 mm. diastolic to as low as 88 mm. systolic and 60 mm. diastolic. His general condition improved slowly, and the heart sounds became less faint. Radiographic examination on October 13, 1931 revealed an enlargement of the heart to the right and left with a prominence at the mid-portion of the left border suggesting the

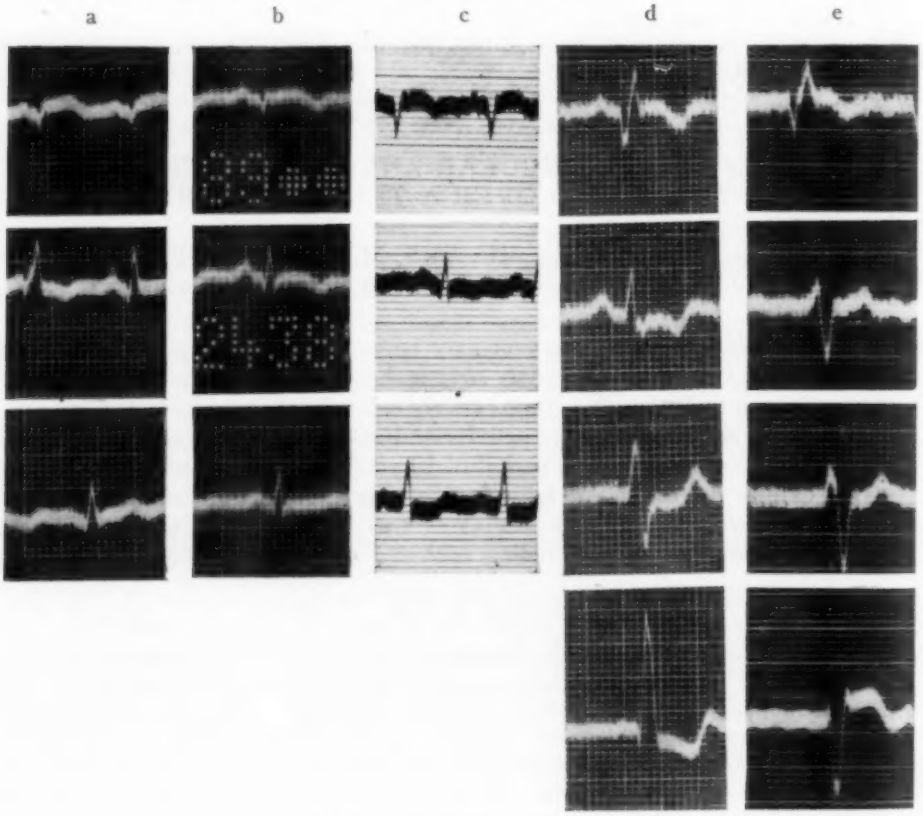

FIG. 1. Electrocardiograms.

1 a. (9/25/31) RT_1 elevation,
Q_1Q_2 present.

1 b. (10/30/31) T_1T_2 inverted,
Q_1Q_2 present.

1 c. (2/29/32) Right axis deviation,
T_1T_2 inverted, RT_2 depressed.

1 d. (10/5/37) Right bundle branch block
(QRS 0.12 second).
Old Lead IV.

1 e. (8/26/41) Bundle branch block.
Added auricular fibrillation.

presence of a ventricular bulge. Ten days later this prominence had increased in size. The electrocardiographic changes were progressive (figure 1 b).

The patient was discharged improved on November 29, 1931, but was rehospitalized nine days later for bilateral bronchopneumonia and congestive heart failure. The course was stormy, requiring a phlebotomy, digitalization and a two and a half week period in an oxygen tent, but thereafter improvement was steady. The electrocardiogram showed no significant change. Radiographic examination revealed an increase in the size of the ventricular bulge which on fluoroscopy was seen to expand outwardly in systole while the rest of the ventricle contracted. The aneurysmal bulge was prominent in the right anterior oblique position, but was not visualized in the left

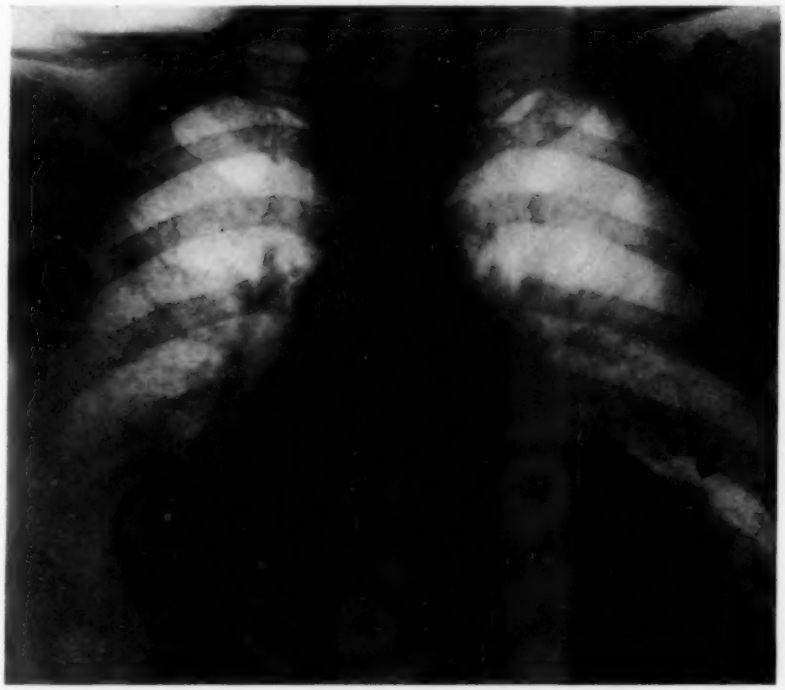

FIG. 2. (2/2/32) Roentgenogram four months after the onset of cardiac infarction. A localized ventricular bulge is noted in the left ventricular contour. The pulmonary changes in the right lower lung field were attributed to pulmonary infarction associated with a slight hydrothorax.

anterior oblique. The impression at this time was that the inflow tract of the left ventricle was not involved in the aneurysmal process.

On January 27, 1932 he was admitted to Montefiore Hospital. Congestive failure was present. The enlarged heart and the disproportion between the forceful apical pulsations and the faint heart sounds suggested the diagnosis of ventricular aneurysm. The decholin circulation time was 21.5 seconds. Therapy consisted of salt-poor, fluid-restricted diet, digitalis, salyrgan, and right thoracenteses.

On fluoroscopy the left ventricle was greatly enlarged and its pulsations were poor. An angular bulge was noted in its upper middle contour. The left auricle was enlarged horizontally. Moderate enlargement of both the outflow and inflow tracts of the right ventricle was present. Four months later there was further enlargement of the left ventricle, especially in the region of the aneurysmal bulge. In

the left anterior oblique view an area of increased density was seen to occupy most of the posterior left ventricular contour. This increased density was believed to be due to an organized thrombus within the aneurysmal bulge.

Four months after admission to Montefiore he was discharged as markedly improved. For the next nine years he was observed frequently in the adult cardiac clinic. Throughout this period he continued his occupation as a machine operator, working 35 hours a week, and traveling to and from his job daily by street car and subway. During the first year salyrgan was given approximately once a month, but thereafter it was no longer necessary since there were no signs of congestive failure.

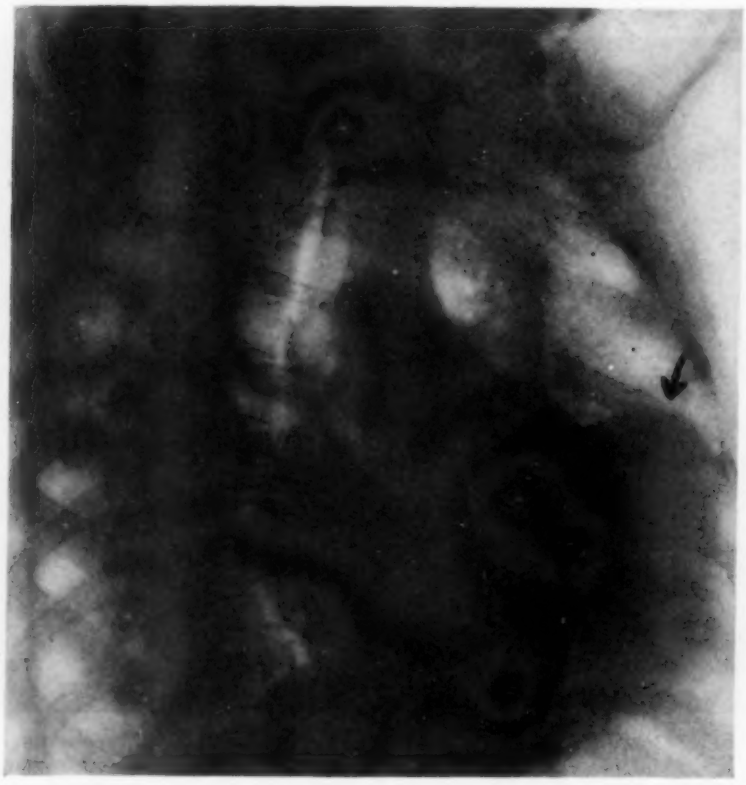

FIG. 3. Right anterior oblique view. The ventricular bulge is noted to project anteriorly and upward.

There were other admissions to the hospital, once for gingival abscesses and twice for treatment of a right renal colic. Except for mild dyspnea he was essentially asymptomatic while he was taking digitalis and ammonium chloride. Beginning in April 1941 he developed severe dyspnea, orthopnea, hepatic enlargement, and edema up to the knees, which became increasingly more difficult to control.

On August 25, 1941 he was admitted to the hospital for the fifth time because of congestive failure. The blood pressure was 102 mm. Hg systolic and 80 mm. diastolic. There were two separate, synchronous, forceful apical pulsations, one in the fourth left interspace 10 cm. from the midsternal line and the other in the fifth, 11 cm. from the midsternal line. The left border was 1 cm. beyond both of these pulsations. The heart sounds were of poor quality and out of proportion to the intensity of the pulsa-

tions. The rate was 60 per minute with frequent ventricular premature contractions. An apical systolic blow was present.

The fluid accumulation responded readily to the usual cardiac régime of bed rest, restriction of fluid and salt, and intravenous mercurials so that after a week he felt quite well and was permitted to walk about. On September 8, 1941 he developed an acute severe colicky pain in the right upper quadrant just above and to the right of the umbilicus. The liver enlarged progressively; sibilant râles were heard throughout the lungs. He responded well to morphine, oxygen and intravenous aminophyllin; the lungs cleared so that by the following day oxygen was no longer necessary. On

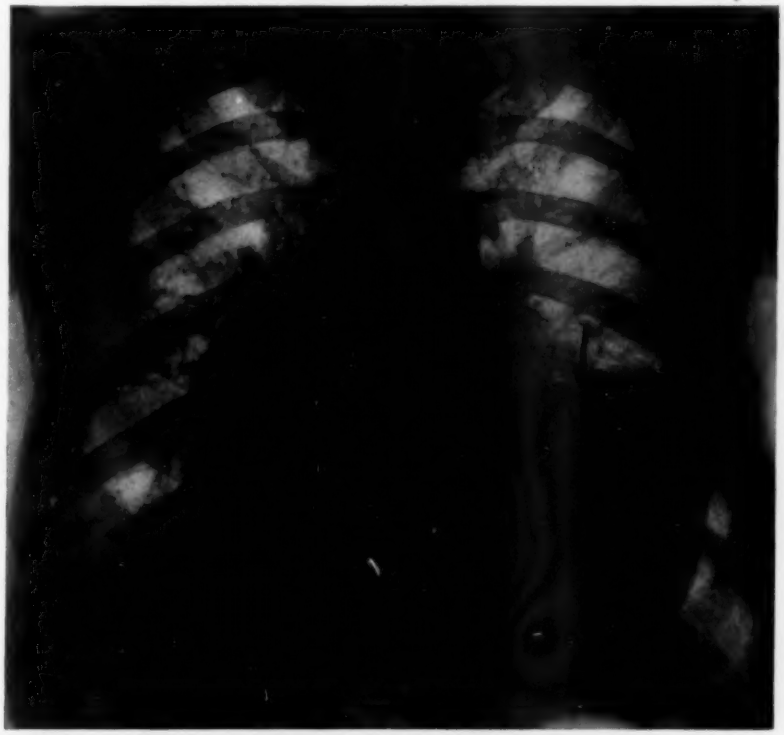

FIG. 4. Same heart 10 years after the onset of cardiac infarction. Calcified plaques were noted in the left lower cardiac contour; a double row of calcification was seen in the original roentgenogram (site indicated by arrows) within the coronary arteries.

September 10 he complained of paraumbilical pain, shortly thereafter became cold, clammy and pulseless, and died 45 minutes later.

Throughout the nine years of observation at Montefiore Hospital radiographic examination demonstrated progressive enlargement of the ventricular aneurysm. The characteristics are described in the captions of figures 2, 3, 4. The electrocardiographic findings are also described with their respective figures (figure 1).

The autopsy diagnosis was: Hypertrophy and dilatation of the heart. Arteriosclerosis of the aorta. Extensive arteriosclerosis of the coronary arteries with old occlusion of the left anterior descending and right main coronary arteries, and marked narrowing of the circumflex branch of the left coronary artery. Old healed infarct of the septum, anterior and posterior walls of the left ventricle with aneurysmal dilatation and mural thrombus formation involving the anterior, lateral, and posterior

walls of this chamber. Obliterative pericarditis. Old healed infarcts of the spleen and kidneys. Chronic passive congestion of the viscera. Pleural effusion, bilateral. Congestion and edema of the lungs.

The heart weighed 869 grams. The pericardial sac was completely obliterated by

FIG. 5. Photograph of unopened anatomical specimen showing the ventricular bulge.

fibrous adhesions. The left ventricle measured 20 to 22 mm. in thickness above the infarcted area; the right ventricle was 4 mm. thick at the apex and 6 mm. thick at the base. The left ventricular wall at the aneurysmal site measured 1 to 3 mm. in thickness and consisted of very dense grayish-brown tissue with little recognizable muscle. It was of the consistency of cartilage and scattered throughout were calcific deposits.

The aneurysmal bulge involved most of the anterior wall of the left ventricle, the greater part of the interventricular septum, and slightly less than the lower half of the posterior wall, mostly laterally. It measured 10 by 8 by 7 cm. and was filled with firm lamellated brown and brownish-red thrombus.

The myocardium of the uninvolved portion of the left ventricle was thick, firm and reddish-brown, with gray fibrous streaks where it joined the infarcted area. The papillary muscles were hypertrophied and contained similar gray fibrous streaks. The

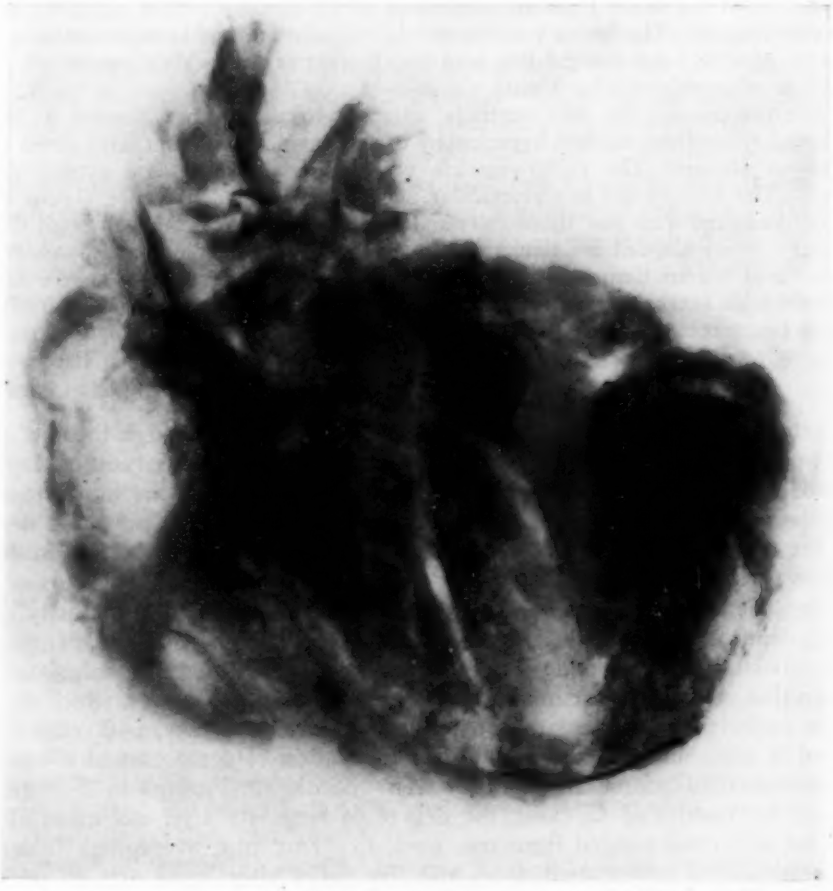

FIG. 6. Roentgenogram of figure 5 indicating the extent of calcification within the left ventricular wall, the organized thrombus, and in the left descending coronary artery.

entire left ventricular chamber was markedly dilated. The right ventricle and both auricles were moderately hypertrophied and dilated. Except for a few atherosclerotic plaques on the mitral and aortic leaflets, all valve rings were normal but moderately dilated. The interventricular septum bulged into the right ventricle especially posteriorly, accentuating greatly the anteroposterior inclination from left to right.

The coronary arteries showed a marked degree of arteriosclerosis with thickening of the walls, atheromata, calcification and extensive occlusion of the two major vessels. The ostium of the left coronary was widely patent but about 1 cm. below, a

point of marked atherosclerotic narrowing was present. The lumen of the anterior descending ramus was completely occluded by firm, gray, fibrous tissue extending for a distance of 2 cm. Save for a small portion of narrowing, the rest of the lumen was occluded down to the infarcted area, where the artery became a calcified and partly ossified solid rod. The larger branches of the anterior descending ramus also revealed marked arteriosclerotic narrowing. There were many sites of moderate to marked narrowing in the left circumflex branch. These were due to plaques which at times reduced the lumen to a mere eccentric slit. The ostium of the right coronary artery was narrowed for about 1 cm. to a diameter of 1.5 mm. by yellow and gray atherosclerotic plaques. The lumen was completely occluded but had been recanalized for a distance of 2 to 3 cm. beyond this area and thereafter was widely patent, with only moderate atherosclerotic narrowing.

Microscopically, the left ventricle adjacent to the infarct showed a fibrous, thickened epicardium, marked hypertrophy of the muscle fibers, and large areas of replacement fibrosis. The right ventricle was similarly though less extensively affected. The wall of the left ventricular aneurysm consisted of dense fibrous tissue, partly hyalinized with few tissue cells and blood vessels. A section through the left coronary artery showed the lumen to be completely occluded by poorly vascularized cellular and fibrous tissue. The wall of this artery was the seat of severe arteriosclerosis with extensive destruction of the media and its replacement by hyalinized fibrous tissue containing plaques of calcium.

Discussion

From the first reported case (Olaus Barrich, 1676 [1]) through those of Galeati [2] and John Hunter [3] in 1757, to the time of Sternberg,[4] aneurysm of the heart existed as a pathological entity. The latter is credited with the first intravitam diagnosis of this condition. Since then numerous papers have appeared describing the method of radiographic and clinical recognition. In the few follow-up studies presented, longevity following the establishment of the diagnosis of ventricular aneurysm has not been a significant factor, and in the majority of reports, death ensued shortly after the diagnosis had been made. Although in a previous study (Gross and Schwedel [5]), based on postmortem analysis, it was shown that ventricular aneurysm does not alter the clinical course, which depends on the underlying hypertensive or arteriosclerotic heart disease, a 10 year survival period is most unusual following this complication of acute coronary occlusion with myocardial infarction. Of the seven who died in Parkinson, Bedford, and Thomson's [6] series of 15 cases, the degree of longevity after diagnosis of ventricular aneurysm ranged from one week to 30 months, averaging 10 months, whereas several others, two, four, and five years after, were able to pursue a comparatively active life. In Dressler and Pfeiffer's [7] 10 reported cases, the duration of life following recognition of the aneurysm varied from three weeks to seven years, those who achieved the upper ranges having been able to carry on normal daily activity or even strenuous physical effort. Ball [8] has reported a patient able to work without marked evidence of cardiac or circulatory failure five and one half years later, and Fulton's [9] two patients lived one and a half and five years after the probable time of aneurysm formation. Berk [10] has followed two cases that have lived for nine years and two for seven years after the initial coronary occlusion or after the development of characteristic radiographic findings of ventricular aneurysm.

So far as could be determined, the case reported here is the longest on record.

In addition to the remarkable longevity, the patient was observed over this 10 year period, and all of the clinical, electrocardiographic, and radiographic findings are available forming a composite picture of almost all such data described in the literature. Although no electrocardiographic tracing typical of ventricular aneurysm exists, Sigler and Schneider [11] reported a pattern of significant corroborative value, i.e., low voltage with the major ventricular deflection being directed upwards in Lead I and downwards in Leads II and III. This is the so-called "aBB pattern" previously described by Winternitz [12] in through and through apical infarction. Gross and Schwedel [5] mention the comparative frequency of progressive deviation of the electrical axis to the right in ventricular aneurysms. Eliaser and Konigsberg [13] have demonstrated an electrocardiographic syndrome present in 27.3 per cent of the S_1 type—a downward major deflection and an inverted T-wave in Lead I, and an upright QRS complex in the third lead, giving a right axis deviation; 36.4 per cent presented a pattern similar to that described by Sigler and Schneider, with or without low amplitude of the ventricular complex in the first lead (S_2, S_3 type); and 18.2 per cent displayed an electrocardiogram of left bundle branch block.

Whether these changes were due to the progressive myocardial changes of an enlarging aneurysm with its organizing and calcifying thrombus, or to changes in conductivity of tissues in contact with the external surface of the heart, or to rotation of the heart around its longitudinal axis cannot be stated.

Summary

A case of ventricular aneurysm is reported, unique both because of a 10 year survival period and the demonstration of almost all the known clinical and laboratory phenomena associated with this condition.

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EDITORIAL

PSYCHOSOMATIC MEDICINE

WHAT is this psychosomatic medicine about which we have been hearing so much in recent years? Is it a brand new medical art or merely a new name for an old art? Surely the latter explanation comes far closer to the truth, for what medical man from the country doctor to the urban ultra-specialist has not on numerous occasions employed the tools of psychosomatic medicine? The success that a given physician may hope to attain in employing these tools will be directly proportional to his interest in psychosomatic concepts, the time that he is willing to devote to the elucidation of such factors, and the amount of common sense with which he is endowed.

As Hinsie succinctly expresses it in the introductory chapter to a current symposium [1] on psychosomatic medicine: "Living as a human being often takes more energy than the daily tasks that gain us a livelihood. It is easier to get settled in an occupation than it is to adjust ourselves to the personal side of people. It is one of the peculiarities of man that when his energies cannot be essentially externalized, they dam up within him, within his mind or body or both. This persistent damming up leads to tension and symptoms. When the symptoms are in the mental sphere, they give rise to special names, such as psychosis and psychoneurosis. When the tensions of living localize themselves in different parts of the body, it appears that the organic part involved is the seat of the trouble, that is, the organ appears "diseased." In a broad sense of the word it is diseased, it is deprived of ease, it is disordered functionally, but the trouble stems from unhappy adjustment to life and not from such organic sources as bacteria, injury, etc. . . . The term pathology is enlarged to include abnormal emotions. Hence, it is said that the organ shows psychopathology."

Psychosomatic complaints manifest themselves in almost any organ or system of the body. The recognition of the true nature of such complaints may require an extensive diagnostic survey in order to rule out true organic disease and thereby serve as a basis for reassurance of the patient. Let us take, for example, the commonplace complaint of *headache*. The busy practitioner may be tempted to pass the complaint off lightly with the advice to take aspirin or some other highly advertised headache remedy. Such preparations will usually afford temporary relief, but the patient will continue to have his headaches. He often becomes convinced that he has sinus trouble or that his eyes are to blame. Therefore, careful examination of the eyes, including refraction and ophthalmoscopic examination, and nose and throat survey, supplemented with sinus roentgenograms, are essential before such local causes can be eliminated to the satisfaction of the patient. In addition

[1] Symposium on psychosomatic medicine, Med. Clin. North Am., W. B. Saunders Co., 1944, p. 525.

to general physical examination, blood count, and urinalysis, a careful neurologic examination, serologic test for syphilis, roentgenogram of the skull and, at times, even ventriculography must be resorted to in order to rule out an organic intracranial basis for the headaches. The characteristics of the headaches—throbbing, squeezing, constricting, drawing, pressing, splitting, localized or generalized—and the circumstances under which they occur will provide the physician with valuable clues as to their true nature. Reënforced with the battery of negative organic findings obtained from the various examinations just enumerated, he is in a more secure position to reassure the patient that his fears or suspicions of a serious organic basis are unjustified and to explore the possibilities of a functional or psychogenic background. It may turn out that the victim is unhappy at his work, working under too much pressure from his boss, burdened with financial or domestic worries (such as a nagging wife or an interfering mother-in-law), or he may be too meticulous in his way of living, constantly upset by trivialities. It is amazing how rapidly and completely tension headaches may clear up following a change in job, improvement in the domestic situation, or adoption of a less perfectionistic outlook on life. Although migraine headaches and so-called "histamine headaches" have been sidetracked through general consent into special categories of their own, the writer is inclined to regard these headaches also as localized vascular outlets (either vasoconstrictory or vasodilatory) for pent-up emotional tension with a definite hereditary pattern in the migraine type.

An equally fruitful field for the psychosomatic approach is to be found in the everyday complaint of *low backache*, especially common in women. And here once more, an extensive diagnostic survey is indicated before we are warranted in concluding that the backache is functional in origin. A detailed history of the development and characteristics of the major complaint, general physical examination, and such special studies as pelvic examination by a competent gynecologist, orthopedic consultation with roentgenograms of the lower spine, and at times cystoscopic study, lumbar puncture, and barium enema should be obtained in order to rule out a local organic cause for the backache. If these special examinations fail to reveal any significant physical abnormality, the physician is justified in suspecting a functional basis for the patient's complaint. It may turn out that the backache is serving as a subconscious (or conscious!) escape from the ardors of housework, the unpleasant prospect of entertaining, or the overzealous onslaughts of Hertzler's "tomcat" husband. Sexual maladjustment is so frequently at the root of chronic backache that it should invariably be considered in cases for which no organic cause can be detected.

Headache and low backache have been selected as two of the most frequently encountered psychosomatic complaints. One could mention many others, among the more common of which are the variegated symptoms of spasticity of the gastrointestinal tract—abdominal pain, vomiting, heartburn,

and diarrhea—which must be differentiated from such organic disorders as ulcer, gall-bladder disease, appendicitis, ileo-colitis, and carcinoma; anxiety attacks with palpitation, dyspnea, and precordial pain to be distinguished from organic heart disease, paroxysmal nocturnal dyspnea, and angina pectoris; psychogenic arthralgias and neuralgias so difficult to separate clinically from true arthritides or neuritides; and functional urinary frequency, hesitancy, and urgency simulating cystitis or other organic disturbances of the genito-urinary tract. The differential diagnosis in all of these conditions rests upon a careful survey of the area involved, followed by an investigation of the personality make-up of the individual concerned, his background, ambitions, frustrations, and tensions; his domestic, religious, and economic problems; his working conditions; his ability to relax and to indulge in healthful recreation. The positive demonstration of a basis for such a psychoneurotic reaction is just as essential for diagnosis as the exclusion of gross organic disease. The trained psychiatrist can be of inestimable assistance to the practitioner or internist in working out the more complicated problems, but there are just not enough psychiatrists to go around, so that the great majority of the psychosomatically afflicted must remain in the lap of their personal physician to "kill or cure" as he sees fit! Many doctors fail to realize how much serious damage they have wrought upon the patient's psyche by such careless remarks as, "You are on the verge of a stroke" or "I cannot be certain whether it is cancer or not." Iatrogenic symptoms may comprise 90 per cent or better of some patients' complaints and may prove most difficult to eradicate.

One note of warning is in order, namely the danger of jumping to the conclusion that a patient's complaints are purely psychogenic and, therefore, failing to carry out procedures essential to differential diagnosis. The psychiatrist, himself, is perhaps more likely to slip into this error than the general clinician who is constantly seeing organic disease as well as functional disorders. Granting that there may be much important psychogenic material in victims of peptic ulcer, ulcerative colitis, asthma, etc., still none but the most analytical-minded of psychiatrists would attempt to treat such patients by psychotherapeutic measures alone.

The importance of the recent emphasis upon psychosomatic medicine must be obvious at a time when human beings everywhere are being subjected to stresses and strains, in both military and civilian life, such as they have never encountered before. The promulgators are to be congratulated upon the timeliness of their efforts with the publication of texts, symposia, and a journal devoted exclusively to psychosomatic medicine. It behooves every physician and surgeon, no matter how broad or narrow his chosen field may be, to familiarize himself with the basic concepts of this science. The therapeutic triumphs that he will gain thereby may far outweigh the victories he wins with drug or scalpel!

W. H. B.

REVIEWS

Clinical Pediatrics. Oxford Medical Outline Series. By I. NEWTON KUGELMASS, M.D., Ph.D., Sc.D. 393 pages; 14.5 × 22 cm. Oxford University Press, New York, N. Y. 1943. Price, $2.00.

This volume follows the trend begun several years ago of presenting subjects in outline form.

The lack of coherence and the close resemblance to a student's notebook give the reviewed book a very limited usage. It is possibly suitable for students preparing for examination and maybe for general practitioners who wish to find information in haste.

The book falls far short of the author's purpose as expressed in the preface to emphasize the determining features of pediatric problems.

J. E. B.

Applied Dietetics. 2nd Edition. By FRANCES STERN. 265 pages; 26 × 18 cm. Williams and Wilkins Company, Baltimore. 1944. Price, $4.00.

This second edition of *Applied Dietetics* is a very concisely put together book. It combines the latest in nutrition research with explanations of therapeutic diets that a beginner can understand. It is a compilation of information of use to the nutritionist, dietitian, doctor, social worker and the like. The book is arranged in four sections, the first devoted to the construction of the therapeutic diet as a deviation from the normal diet, the second is a series of tables to simplify the computation of the diet, the third is devoted to dietary outlines for the treatment of most common diseases, and the fourth part to typical diets and menus.

Miss Stern's development of the therapeutic diet from the normal diet in relation to the body needs and capabilities is an excellent introduction for the student who is interested in seeing why such special diets are needed. The emphasis is on the patient as an individual. It explains the methods of gaining patient coöperation and how to explain a therapeutic diet as a modification of the normal.

The second section of the book is entirely in tabular form and to gain the maximum advantage from it would take considerable time. However, I believe that if the reader were thoroughly familiar with the tables, the time saving factor in computing therapeutic diets to meet nutrition standards would be of great advantage.

Complete dietary outlines which consist of the dietary treatment of 23 diseases and abnormal conditions make up the third section. Each outline considers the body part affected, the normal and pathological physiology, the dietary treatment and contributing factors, food for the day, the reason for the selection of foods used, and the education of the patient as to his condition and dietary treatment.

The fourth section is the practical application of the third section which suggests meal plans and evaluates these meal plans for the necessary food constituents.

To understand Miss Stern's book requires that the reader be well educated in physiology and nutrition. It will be of chief value for reference material for those interested in dietary treatment of diseases and of much value in instructing the patient as to his own particular needs. The first section of the book is much simpler to understand than the remainder and might well be used as the basis for instructing patients who do not have all the scientific background of professional people who are chiefly interested in the scientific facts which make up the last three sections.

H. B.

BOOKS RECEIVED

Books received during May are acknowledged in the following section. As far as practicable, those of special interest will be selected for review later, but it is not possible to discuss all of them.

Clinical Evaluation of the Rehabilitation of the Tuberculous. By LOUIS E. SILTZBACH, M.D. 70 pages; 23.5 × 15.5 cm. 1944. National Tuberculosis Association, 1790 Broadway, New York 19, N. Y. Price, $1.00 cloth-bound; $.50 paper cover.

Notes on Nursing by a Nurse. By SARAH CORRY, R.N. 144 pages; 19.5 × 13 cm. 1944. D. Appleton-Century Co., 35 W. 32nd St., N. Y., N. Y. Price, $1.50.

Intracranial Arterial Aneurysms. By WALTER E. DANDY. 147 pages; 24 × 16 cm. 1944. Comstock Publishing Company, Inc., 124 Roberts Place, Ithaca, N. Y. Price, $2.50.

Manual of Human Protozoa. By RICHARD R. KUDO, D.Sc. 125 pages; 20 × 13 cm. 1944. Charles C. Thomas, Springfield, Ill. Price, $2.00.

Practical Malaria Control. A Handbook for Field Workers. By E. M. GUNTHER, M.D., B.S., D.T.M. (Sydney). Foreword by PROF. HARVEY SUTTON, O.B.E., M.D., F.R.A.C.P., B.Sc., D.P.H., F.R. San.I. 91 pages; 20 × 13.5 cm. 1944. Philosophical Library, Inc., 15 E. 40th St., N. Y., N. Y. Price, $2.50.

The Treatment of Peptic Ulcer. By GEORGE J. HEUER, M.D. Assisted by CRANSTON HOLMAN, M.D., and WILLIAM A. COOPER, M.D. 118 pages; 23.5 × 16 cm. 1944. J. B. Lippincott Company, Philadelphia. Price, $3.00.

Radiation and Climatic Therapy of Chronic Pulmonary Diseases. Edited by EDGAR MAYER, M.D., F.A.C.P., F.A.C.C.P., with the collaboration of 22 other contributors. 393 pages; 23.5 × 16 cm. 1944. Williams & Wilkins Company, Baltimore. Price, $5.00.

The Management of Neurosyphilis. By BERNHARD DATTNER, M.D., Jur.D., with the collaboration of EVAN W. THOMAS, M.D., and GERTRUDE WEXLER, M.D. Foreword by JOSEPH EARLE MOORE, M.D. 398 pages; 23.5 × 16 cm. 1944. Grune & Stratton, Inc., New York, N. Y. 1944. Price, $5.50.

Intravenous Anesthesia. By R. CHARLES ADAMS, M.D., C.M., M.S.(Anes.). 663 pages; 24 × 16 cm. 1944. Paul B. Hoeber, Inc., New York. Price, $12.00.

The Principles and Practice of Tropical Medicine. Part I—Dealing with nearly all the major tropical diseases. By L. EVERARD NAPIER, C.I.E., F.R.C.P. 522 pages; 25.5 × 17 cm. 1943. Thacker, Spink & Co., Ltd., Calcutta; W. Thacker & Co., London. Price, 25 rupees.

The Use of Penicillin in Treating War Wounds. Instructions prepared by the Penicillin Clinical Trials Committee. Medical Research Council War Memorandum No. 12. 16 pages; 24.5 × 15.5 cm. 1944. His Majesty's Stationery Office, York House, Kingsway, London, W. C. 2. Price, $.10. (Code No. 45–9999.)

The Control of Cross Infection in Hospitals. Memorandum prepared for the Committee on Preventive Medicine of the Medical Research Council by the Sub-Committee on Cross Infection in Hospital Wards. Medical Research Council War Memorandum No. 11. 34 pages; 24.5 × 15.5 cm. 1944. His Majesty's

Stationery Office, York House, Kingsway, London, W. C. 2. Price, $.15. (Code No. 45–9–11.)

Polinosis. By LEOPOLDO HERRAIZ BALLESTERO (Doctor en Medicina) and JUAN VICTOR MONTICELLI (Doctor en ciencias naturales). 227 pages; 23 × 16 cm. 1943. Libreria Hachette S. A., Palacio del Libro, Buenos Aires.

Anemopolinologia Aplicada. By MIGUEL AGUSTIN SOLARI. 54 pages; 26.5 × 18 cm. 1942. Libreria Hachette S. A., Palacio del Libro, Buenos Aires.

Sueroterapia por Nebulizacion. Tesis de Doctorado. By ANDRES MARTINEZ MARCHETTI. 47 pages; 26.5 × 18 cm. 1942. Libreria Hachette S. A., Palacio del Libro, Buenos Aires.

Valor Diagnostico de Ciertos Sintomas de Alergia Menor. Estudio Estadístico de las Manifestaciones Sintomáticas de la Alergia en la Zona de la Capital Federal. By BENIGNO R. GARAT. 44 pages; 27 × 18 cm. 1943. Libreria Hachette S. A., Palacio del Libro, Buenos Aires.

COLLEGE NEWS NOTES

Additional A.C.P. Members in the Armed Forces

Previously reported in the News Notes section of this journal were the names of 1,699 Fellows and Associates of the College on active military duty. The following additional members have since reported for active duty, bringing the total to 1,701.

John A. Baird
Albert M. Eaddy

Notice has been received that Lt. Comdr. Roland N. Klemmer, (MC), USNR. F.A.C.P., of Lancaster, Pa., died in the South Pacific on May 9, 1944, of a heart ailment.

Major Erle B. Craven, Jr., (MC), AUS, was retired to inactive service on December 14, 1943, and has resumed the practice of medicine at Lexington, N. C., and teaching at Duke University.

Captain Louis Friedfeld, (MC), AUS—honorably discharged, April 29, 1944.

New Life Members of the College

The following Fellows, listed in the order of subscription, have become Life Members of the College:

Dr. Thomas T. Holt, Wichita, Kans.
Dr. Thomas Donald Cunningham, Denver, Colo.
Dr. Henry K. Speed, Sayre, Okla.

Gifts to the College Library

The following gifts are graciously accepted:

Books

Dr. Louis E. Siltzbach (Associate), New York, N. Y.—"Clinical Evaluation of the Rehabilitation of the Tuberculous."

Reprints

Lewis H. Bronstein (Associate), Captain, (MC), AUS—2 reprints.
Abraham G. Cohen (Associate), Major, (MC), AUS—1 reprint.
Dr. Barnett Greenhouse, F.A.C.P., New Haven, Conn.—1 reprint.
Ellis H. Hudson, F.A.C.P., Commander, (MC), USNR—1 reprint.
Alfred L. Kruger (Associate), Captain, (MC), AUS—1 reprint.
Dr. Robert C. Moehlig, F.A.C.P., Detroit, Mich.—1 reprint.
Dr. Ellen C. Potter, F.A.C.P., Trenton, N. J.—1 reprint.
Dr. William B. Rawls, F.A.C.P., New York, N. Y.—1 reprint.
George F. Schmitt, Jr., F.A.C.P., Lieutenant, (MC), USNR—1 reprint.
Maurice A. Schnitker, F.A.C.P., Major, (MC), AUS—2 reprints.
Dr. Maurice S. Segal, F.A.C.P., Boston, Mass.—2 reprints.
Dr. Isaac J. Silverman, F.A.C.P., Washington, D. C.—1 reprint.
Dr. Alexander S. Wiener, F.A.C.P., Brooklyn, N. Y.—5 reprints.

A.C.P. Members in Mississippi Held Luncheon Meeting

Under the Governorship of Dr. John G. Archer, F.A.C.P., the annual luncheon of the Mississippi members of the American College of Physicians was held May 9, at the Robert E. Lee Hotel, Jackson, Miss., during the annual meeting of the Mississippi State Medical Association. Dr. William C. Chaney, F.A.C.P., Governor of the College for Tennessee, gave an address on the Wagner-Murray-Dingell Bill, and Major George M. Knowles, (MC), AUS, F.A.C.P., presented a paper on Arthritis. There was a round-table discussion after each address. The meeting was most successful and the attendance good.

Captain Richard A. Kern, F.A.C.P., Received Citation

Captain Richard A. Kern, (MC), USNR, formerly of Philadelphia, received the following citation from Admiral W. F. Halsey for services as set forth below:

"For meritorious and efficient performance of duty while serving as Medical Consultant on the Staff of the Commander South Pacific Area and South Pacific Force during the period from August, 1943, to February, 1944. Captain Kern, in discharging his duties, made his services available to every medical officer in the South Pacific Area, visiting every medical facility many times. He traveled throughout the forward and combat areas, and worked with the medical officers in the front line of combat operations on Bougainville, British Solomon Islands. At all times his objective was to improve the treatment of the sick and wounded, and no undertaking was too great, nor any detail too small, to bring forth his best efforts toward that end. His tireless endeavors, professional ability and devotion to duty were in keeping with the highest traditions of the United States Naval Service."

Captain Kern has been returned to the United States, and is now serving as Chief of Medicine at the United States Naval Hospital, Philadelphia.

Major Dickinson Sergeant Pepper, (MC), AUS, F.A.C.P., has been advanced to Chief of Medicine at the McGuire General Hospital, Richmond, Va.

Woman's Medical College of Pennsylvania Organizes Postgraduate Courses in Pre-Clinical Sciences

The Woman's Medical College of Pennsylvania at Philadelphia organized in the autumn of 1943 a postgraduate course for the review of the pre-clinical sciences, the course being given throughout the fall, winter, and spring of 1943 and 1944. The faculty was made up very largely from the faculty of the Medical College. The course was attended by a group ranging from 25 to 45 throughout the year, many of them taking advantage of the course to prepare for the examinations of the American Board of Internal Medicine. Physiology and physiological chemistry were among the most popular subjects.

The review course in the pre-clinical subjects will not be repeated until 1946, but the same group will continue in the autumn of 1944 in review work in clinical subjects, such as parasitology, electrocardiography, roentgenology and tuberculosis.

Dr. William G. Leaman, Jr., F.A.C.P., Professor of Medicine, Woman's Medical College, has largely directed the organization of the course.

Dr. Frank H. Krusen, F.A.C.P., Rochester, Minn., and Dr. Andrew C. Ivy, F.A.C.P., Chicago, Ill., are Chairman and member, respectively, of the Scientific Advisory Committee of the Baruch Committee on Physical Medicine, recently an-

nounced in these pages. The offices of the Committee, which was created by a recent gift of $1,100,000.00 from Mr. Bernard M. Baruch, are at 597 Madison Ave., New York City. Miss Grace Keef, Executive Secretary, will supply to those asking for it, copies of the report on which Mr. Baruch based his donation.

Dr. Charles M. Griffith, F.A.C.P., Washington, D. C., Medical Director of the United States Veterans Administration, Lt. Col. Howard A. Rusk, (MC), AUS, F.A.C.P., Chief of the Convalescent Division, Office of the Air Surgeon, War Department, and Captain Howard Montgomery, (MC), USN, F.A.C.P., Chief of Rehabilitation, Bureau of Medicine and Surgery, Navy Department, Washington, D. C., have been appointed members of the Committee on War and Post-War Physical Rehabilitation and Reconditioning.

Colonel Charles F. Craig, F.A.C.P., Emeritus Professor of Tropical Medicine, Tulane University of Louisiana, recently received the Theobald Smith Gold Medal of the George Washington University School of Medicine, in recognition of his contributions in the field of Tropical Medicine.

Blakiston Company, medical publishers, Philadelphia, has recently been acquired by Doubleday-Doran & Company, Inc. The Blakiston Company, however, will continue its present publication business under its original name and under the direction of its former President, Mr. Horace G. White, and the entire personnel.

Lt. Comdr. Harold J. Harris, (MC), USNR, F.A.C.P., addressed the New York Society for Clinical Ophthalmology, May 1, 1944, on the subject of brucellosis in ophthalmology.

Brigadier General James Stevens Simmons, (MC), USA, F.A.C.P., Chief of the Preventive Medicine Service, Office of the Surgeon General, U. S. Army, has been elected a member of the Council on Industrial Health of the American Medical Association.

On May 17, at the invitation of the Cuban Government and Dr. Alberto Recio, Minister of Health, Brigadier General Simmons visited Havana and took part in the dedication of the new National Institute of Health. In the course of the ceremonies, President Batista decorated General Simmons with the Medal of the Carlos J. Finlay National Order of Merit in the grade of Gran Official. The President also transmitted by General Simmons to Major General Norman T. Kirk, F.A.C.P., Surgeon General of the U. S. Army, a certificate conferring the Carlos J. Finlay Order of Merit in the grade of Gran Cruz on the former American Yellow Fever Commission for its fundamental experimental work in Cuba on the etiology and transmission of yellow fever under the leadership of Major Walter Reed. The certificate will be preserved in the Army Medical Library in Washington.

Dr. Edward B. Krumbhaar, F.A.C.P., Professor of Pathology, University of Pennsylvania School of Medicine and Graduate School of Medicine, Philadelphia, was recently made an Honorary Fellow of the Royal Society of Medicine.

Dr. J. C. Geiger, F.A.C.P., Director of Public Health of the City and County of San Francisco, Calif., has been honored by the Government of Ecuador, by the grant of its exalted decoration, "Al Merito," with the citation, "For distinguished service, for noteworthy and indomitable leadership in the advancement of public health in the Americas."

The Desert Sanatorium of Southern Arizona, Tucson, has discontinued operations after many years of service.

Dr. Roland Davison, F.A.C.P., its Medical Director, has removed to 516 Sutter St., San Francisco 2, Calif., where he will engage in the practice of Internal Medicine.

Dr. Floyd L. Rogers, F.A.C.P., Lincoln, was installed as President of the Nebraska State Medical Association at its recent meeting in Omaha, May 1–4.

Dr. Wallace M. Yater, F.A.C.P., Washington, D. C., has been confirmed as the official appointee of the American College of Physicians in the Division of Medical Sciences, National Research Council, for a three-year term beginning July 1, 1944.

Dr. Barnett Greenhouse, F.A.C.P., New Haven, addressed the New Haven Medical Association, May 17, on "Current Trends in Diabetes Mellitus."

Announcement was recently received of the advancement of Dr. Francis C. Wood, F.A.C.P., to the rank of Lieutenant Colonel in the Medical Corps of the Army. He is on duty in India.

A recent announcement confirmed that the following Fellows of the College attached to the Office of the Surgeon General of the U. S. Army have been promoted in rank, as indicated:

George F. Lull, from Brigadier General to Major General;
Leon A. Fox, from Colonel to Brigadier General;
Shelley U. Marietta, from Brigadier General to Major General.

Colonel Baldwin L. Keyes, (MC), AUS, F.A.C.P., head of the Jefferson Base Hospital, Philadelphia, Pa., was recently in Philadelphia after service in North Africa.

Captain Albert Soiland, (MC), USNR, F.A.C.P., attended the First National Mexican Cancer Congress at Guadalajara, last November, as the authorized delegate from the Bureau of Medicine and Surgery of the U. S. Navy, the American College of Radiology, the American Radium Society, the American Roentgen Ray Society and the American Society for the Control of Cancer.

Captain Soiland was recently notified that he had been appointed Honorary Professor on the faculty of the University of Guadalajara.

Dr. Robert S. Berghoff, F.A.C.P., Chicago, who became Acting President of the Illinois State Medical Society last March, following the death of President George Post, was elected President-Elect of the Society at its recent annual meeting in Chicago. He will serve as President-Elect 1944–45, and as President for 1945–46.

War, Rehabilitation and Civilian Surgery will be the theme of the Ninth Annual Assembly of the International College of Surgeons at Philadelphia, October 3–5, 1944, with headquarters at the Benjamin Franklin Hotel.

The Twelfth Annual Graduate Short Course for Doctors of Medicine, under the auspices of the Graduate School of the University of Florida, the Florida Medical

Association and the Florida State Board of Health, was held at Jacksonville, June 19–24. The course covered the subjects of pediatrics, obstetrics, gynecology, venereal diseases, medicine, surgery and post-war public health.

Dr. T. Z. Cason, F.A.C.P., Jacksonville, is the Director of the Postgraduate Committee. Dr. George L. Cook, F.A.C.P., Tampa, and Dr. W. Wellington George, F.A.C.P., West Palm Beach, are members of the Committee.

Dr. Raphael Isaacs, F.A.C.P., Chicago, will be the Medical Director of the newly incorporated Hematology Research Foundation. The Foundation has been set up and is being financed by prominent lay persons, and one of the first problems for investigation will be a study of leukemia.

Dr. Edward L. Tuohy, F.A.C.P., Duluth, has been elected President of the Minnesota State Medical Association. Dr. Sidney A. Slater, F.A.C.P., Worthington, and Dr. J. Arnold Bargen, F.A.C.P., Rochester, are Vice-Presidents. Dr. Benjamin B. Souster, F.A.C.P., St. Paul, is the Secretary.

Dr. Stockton Kimball, F.A.C.P., Associate in Medicine and Pharmacology, and Dr. Lawrence E. Hummel, F.A.C.P., Assistant Dean and Assistant Professor of Medicine, University of Buffalo School of Medicine, have returned from a study of malaria and other tropical diseases in Guatemala.

On May 18, Dr. William H. Sebrell, Jr., F.A.C.P., Chief of the Division of Chemotherapy, National Institute of Health, delivered the eighth Harvey Society Lecture of the New York Academy of Medicine, on "The Relation Between Sulfonamide Drugs and Vitamin Deficiencies."

The late Dr. Charles W. Burr, F.A.C.P., Emeritus Professor of Mental Diseases, University of Pennsylvania, bequeathed $200,000.00 to the endowment fund of the University; also left his library of some 19,000 volumes to the University Library.

Dr. Joseph McFarland, F.A.C.P., Philadelphia, completed in the early spring a medical lecture tour of Costa Rica and Central America.

Dr. Harry C. Schmeisser, F.A.C.P., has resigned as Chief of the Division of Pathology at the University of Tennessee College of Medicine, but he will continue as Professor of Pathology.

Dr. Edward L. Turner, F.A.C.P., President of Meharry Medical College, Nashville, Tenn., recently announced a grant by the General Education Board of the Rockefeller Foundation of $4,000,000 for endowment and $300,000 for a contingent fund for the above institution.

Dr. William C. Chaney, F.A.C.P., Governor of the College for Tennessee, has been elected President-Elect of the Tennessee State Medical Association.

Dr. Ernest R. Zemp, F.A.C.P., Knoxville, was reëlected for the twenty-first consecutive year as speaker of the Association's House of Delegates.

The following Fellows of the College gave a radio broadcast in connection with the Doctors at War program of the American Medical Association, as indicated below:

Major General George F. Lull, (MC), USA, Washington, D. C.—June 3, 1944, "Medicine in the Front Lines";
Dr. James E. Paullin, Atlanta, Ga.—June 11, 1944, "War and the Medical Profession";
Colonel W. Paul Holbrook, (MC), AUS, Air Surgeon's Office—June 13, 1944, "Rheumatic Fever in the Army Air Forces";
Lieutenant Colonel Howard A. Rusk, (MC), AUS, Air Surgeon's Office—June 13, 1944, "Convalescent Training Program in Army Air Forces Hospitals";
Brigadier General James S. Simmons, (MC), USA, Washington, D. C.—June 17, 1944, "Mechanized Dandruff."

Dr. Frank J. Milloy, F.A.C.P., Phoenix, was named Secretary of the Arizona State Medical Association at its annual meeting in April.

A reading room at St. Luke's Hospital has been dedicated to Dr. Arthur R. Elliott, F.A.C.P., Senior Consulting Physician. Dr. Elliott was responsible for obtaining funds to develop the Library.

Dr. Buell H. Van Leuven, F.A.C.P., Traverse City, Michigan, has been appointed Health Director of Chippewa County, and will have his headquarters in Sault Ste. Marie.

Dr. Frederick R. Taylor, F.A.C.P., Associate Professor of Clinical Medicine, Bowman Gray School of Medicine, Winston-Salem, has been named Professor of Medical Literature, a newly created position. A course is being devised to give instruction in the relative value of various publications, ethics of medical writing, editing of medical papers, methods of keeping abreast of medical literature, etc.

Dr. Edgar McNamee, F.A.C.P., Cleveland, has been made President-Elect of the Ohio State Medical Association.

Under the presidency of Dr. Karl J. Henrichsen, F.A.C.P., the American Academy of Tuberculosis Physicians held its annual meeting at Chicago, June 13.

Dr. Walter P. Gardner, F.A.C.P., for several years Superintendent of the Anoka State Hospital, recently resigned and will return to private practice in St. Paul, Minn.

Dr. Jay C. Davis, F.A.C.P., Minneapolis, has been elected Vice-President of the Minneapolis Academy of Medicine.

Dr. Francis E. Harrington, F.A.C.P., Commissioner of Health of Minneapolis, has been elected President of the Minnesota Public Health Association to succeed Dr. Sidney A. Slater, F.A.C.P., Worthington.

Dr. Marvin L. Graves, F.A.C.P., Houston, recently received the honorary degree of Doctor of Science, conferred by Baylor University.

Dr. Harry A. Durkin, F.A.C.P., Peoria, has been elected President of the Illinois Heart Association.

Dr. Phillip H. Jones, Jr., F.A.C.P., New Orleans, has been elected a Vice-President of the Louisiana State Medical Society.

Under the presidency of Dr. Joseph T. Beardwood, Jr., F.A.C.P., Philadelphia, the American Diabetes Association held its fourth annual meeting at Chicago, June 11.

Colonel Leonard G. Rowntree, (MC), AUS, F.A.C.P., delivered the Banting Memorial Lecture on "Experiences of the Selective Service System with Glycosuria."

The Association for the Study of Internal Secretions, under the presidency of Dr. E. Kost Shelton, F.A.C.P., Los Angeles, held its twenty-seventh annual meeting in Chicago, June 12–13. Among the guest speakers were Dr. Maurice Fremont-Smith, F.A.C.P., Boston, and Dr. Willard O. Thompson, F.A.C.P., Chicago.

The American Society of Clinical Pathologists held its twenty-third annual meeting in Chicago, June 8–11, under the presidency of Dr. Walter S. Thomas, F.A.C.P., Rochester, N. Y.

Colonel James E. Ash, F.A.C.P., curator of the Army Medical Museum, Washington, D. C., conducted a seminar on "Pathology of Tropical Diseases"; Dr. Israel Davidsohn, F.A.C.P., Chicago, was the moderator.

The forty-fifth annual meeting of the American Therapeutic Society was held in Chicago, June 10, under the presidency of Dr. William V. Watson, F.A.C.P., Toronto, Ontario.

The forty-sixth annual meeting of the American Gastroenterological Association, under the presidency of Dr. Sara M. Jordan, F.A.C.P., Boston, was held in Chicago, June 12–13. At the annual dinner meeting the Friedenwald Medal was presented to Dr. Anton J. Carlson, F.A.C.P., Emeritus Professor of Physiology at the University of Chicago School of Medicine, and to Dr. Andrew C. Ivy, F.A.C.P., Professor of Physiology and Pharmacology at Northwestern University Medical School.

Dr. Thomas Parran, F.A.C.P., Washington, D. C., has received a re-appointment as Surgeon General of the U. S. Public Health Service for another term of four years.

Dr. A. Austin Pearre, F.A.C.P., and Dr. John S. Derr, F.A.C.P., both of Frederick, have been elected President and Second Vice-President, respectively, of the Frederick County (Md.) Medical Society.

Dr. Cecil O. Patterson, F.A.C.P., and Dr. Merritt B. Whitten, F.A.C.P., have been elected Secretary and Treasurer, respectively, of the Dallas Southern Clinical Society.

Dr. Whitten has also been elected President of the Texas Club of Internists.

Dr. Neil D. Buie, F.A.C.P., Marlin, Tex., is Vice-President of the Federation of the State Boards of the United States.

Dr. James Alexander Miller, M.A.C.P., a former President of the American College of Physicians and of the National Tuberculosis Association, was awarded the Trudeau Medal for meritorious achievement in the prevention and treatment of tuberculosis at the last meeting of the National Tuberculosis Association in Chicago, May 10.

Dr. Arthur Grollman, F.A.C.P., heretofore research professor of medicine and associate professor of physiology and pharmacology at the Bowman Gray School of Medicine, Winston-Salem, N. C., has accepted an appointment as professor of experimental medicine at the Southwestern Medical College, Dallas, beginning July 1.

New Edition of Directory of Medical Specialists to Be Published

The third edition of the Directory of Medical Specialists listing names and biographic data of all men certified by the fifteen American Boards is to be published early in 1945. Collection of biographic data of the Diplomates certified since the 1942 edition, and revision of the older listings in that volume, are now going forward rapidly. Diplomates are requested to make prompt return of notices regarding their biographies as soon as possible after receiving the proper forms from the publication office soon to be mailed to them.

WAR-TIME GRADUATE MEDICAL MEETINGS

Region No. 3 (New York)—Dr. O. R. Jones, Chairman; Dr. N. Jolliffe, Dr. H. W. Cave.

Rhoads General Hospital, Utica, New York

July 20 Blood and Blood Substitutes: Their Indications and Uses—Dr. Frederick Marty

August 17 Wounds of the Extremities and Their Management—Dr. Roscoe Severance

Region No. 5 (Maryland, District of Columbia, Virginia, West Virginia)—Dr. J. A. Lyon, Chairman; Dr. C. R. Edwards, Dr. G. L. Weller.

United States Naval Hospital and United States Naval Academy Dispensary, Annapolis, Maryland

July 21 Drug Allergies—Dr. Nathan B. Herman

Region No. 14 (Indiana, Illinois, Wisconsin)—Dr. W. O. Thompson, Chairman; Dr. N. C. Gilbert, Dr. W. H. Cole.

Mayo General Hospital, Galesburg, Illinois

July 19 Peripheral Vascular Diseases
- *a.* Diagnosis and Conservative Treatment
- *b.* Surgical Treatment

Camp Ellis, Illinois

July 19 High Blood Pressure
- *a.* Pathological—Physiological Basis—Conservative Therapy Renal Extracts
- *b.* The Surgical Treatment

Camp McCoy, Wisconsin

July 19 Conditions Affecting Glucose Metabolism
- *a.* Endocrine—Pituitary—Thyroid—Adrenal—Pancreatic
- *b.* Renal, Alimentary, Hepatic. Diff. Diagnosis and Treatment

Camp Grant, Illinois

July 19 Diseases of the Intestinal Tract
- *a.* Regional ileitis, colitis, diverticulitis. Diagnosis and Treatment.
- *b.* Dysentery—Amebic and Bacillary.
- *c.* Malignancies

Truax Field, Wisconsin

July 19 Dermatological Diseases
Clinic with Presentation of Cases and Slides. Diagnosis and Treatment.
- *a.* The Less Common Venereal Diseases
Lymphogranuloma Venereum, Granuloma Inguinale, Chancroid, Yaws—Slides—Diagnosis and Treatment.

Scott Field, Illinois

July 19 Malignancies in the Army Age Group
- *a.* Melanomata
- *b.* Teratomata
- *c.* Lymphoblastomata

Chanute Field, Rantoul, Illinois

July 19 Virus and Rickettsial Diseases
- *a.* Virus diseases
- *b.* Rickettsial diseases

Lieutenant General Robert Kho-sheng Lim, Chief of the Supervising and Planning Commission of the Chinese Army Medical Service, who has recently arrived in this country on a military mission, has given an interesting account of the methods used to meet China's critical shortage of trained medical personnel. This shortage is described by General Lim as "the Chinese Army's most serious medical problem." In Free China today, there are only about 6,000 fully trained physicians, he said. Only 3,000 of these are serving with the Chinese Army. To meet this shortage, eight thousand young Chinese men and women, many of them only 17 years of age and none over 25, are carrying the burden of medical treatment of wounded Chinese soldiers. These young people are known as junior medical aides, and go into the field after intensive training of six and even only three months.

The training of these medical aides is accomplished in six Emergency Service Training Schools which were organized partly with funds supplied by the American Bureau for Medical Aid to China and which are today being supported by funds obtained by United China Relief through the National War Fund. Only the most basic medical training and instruction in only the most common diseases can be given to the junior medical aides, since the need for their services is so great, Dr. Lim said. The training consists of instruction in first aid, in setting bones and treating fractures, in immunization, in preventive medicine and in general sanitation.

The efficacy of their training and the young people's efficiency in putting into practice their limited medical knowledge is shown partly by the fact that there has been no major epidemic in the Chinese Army or in China for six years.

The Emergency Medical Service Training Schools graduates go into small towns or villages near the front lines, and set up medical stations and dispensaries. "Civilians and soldiers alike are given medical treatment," said General Lim, "because in areas where the Chinese soldiers depend for food and other necessities upon the local population, and especially when they remain over long periods in one area, the good health of the civilians is essential. Many backward villages which never before had medical service of any kind, are now receiving it."

Shortage of equipment must often be handled with new methods, such as those used in vaccinations. In normal medical practice, an individual ampule of vaccine is used for each person. But because it is impossible to obtain materials for large quantities of ampules, the Chinese Army Medical Service is using large ampules containing sufficient vaccine for 100 vaccinations, and is administering to groups of 100 at a time.

General Lim organized the Chinese Red Cross Medical Relief Corps in 1937, and created hundreds of mobile operating units, known as "hospitals on muleback," which for seven years have operated as near as a half mile to the fighting lines. Last June, General Lim was awarded the Legion of Merit by President Roosevelt.

Fund for Research in Psychosomatic Medicine

The National Committee for Mental Hygiene announces the establishment of a fund for research in psychosomatic medicine to stimulate and subsidize research in the psychosomatic aspects of the diseases chiefly responsible for disability and death. The fund will be directed by Dr. Edward Weiss, Philadelphia, and administered under the direction of Dr. George S. Stevenson, New York, medical director of the National Committee for Mental Hygiene. Projects will be considered by a committee composed of Drs. Charles A. Aldrich, Rochester, Minn., Franz Alexander, Chicago, Stanley Cobb, Boston, John Romano, Cincinnati, and Lieut. Col. William C. Menninger. Additional information may be obtained from Dr. Weiss, 269 South 19th Street, Philadelphia 3.

The program for the Annual Meeting of the Association of Military Surgeons of the United States to be held at the Pennsylvania Hotel, New York City, November 2 to 4, incl., is being rapidly completed. In addition to addresses by the Surgeons General of the Army, Navy, and U. S. Public Health Service and by other distinguished guests, there will be formal papers, panel discussions and scientific and technical exhibits on the latest advances in military medicine.

Doctor Draft May Endanger U. S. Health

Atlanta, Ga.—Dr. James E. Paullin, retiring president of the American Medical Association, in a nationwide CBS radio broadcast during the program, "The Doctor Fights" (June 6) warned against "an alarming situation" in medicine, seriously threatening the public health, because so many doctors are in the armed forces and it is difficult to obtain draft deferments for premedical students. Dr. Paullin asserted that "so hazardous is this situation as it relates to the health and welfare of the American people that several special committees of the American Medical Association are working seriously on this problem right now."

He pointed out that, in age groups over 45, "there are now more deaths among doctors than statistics would lead us to expect—simply because of the excessive strain placed upon these doctors by today's difficult times."

"Today with more than 60,000 doctors in the armed forces and with the Army and Navy taking more than half of the new graduates each year, an alarming situation has developed which in the future may seriously threaten the public health," he said.

"About 3,600 doctors are entering the armed services annually. There is an annual deficit each year of at least 2,200 doctors, because the vacancies created in medical ranks by death or forced retirement from practice because of age or illness cannot be filled. The reason for this lies in the difficulty of deferring premedical students, and in keeping our classes filled with otherwise draft-exempt men or with women.

"The problems of medical care are fundamental to the reconstruction and rehabilitation of our nation in the postwar period," he said. "The medical profession of this nation is willing to take the lead in planning the evolutionary changes that are bound to occur."

Medicine's most important current problem, Dr. Paullin asserted, "is the maintenance of a constant flow of physicians from our medical schools to supply the civilian population and the armed forces now and in the postwar period."

"The education of a modern doctor," he explained, "requires a period of premedical education. Even when it is accelerated to the utmost, it takes a year and a half. Then comes medical education which, even when speeded to the greatest rate, requires two and one-half years additional. Besides every doctor must have, even in wartime, at least nine months of internship in a good hospital. In peacetime this may be a year or even two years of additional training."

OBITUARIES

DR. VIRGIL EARL SIMPSON

Dr. Virgil Earl Simpson, F.A.C.P., an outstanding Internist of the South, died in Louisville, Kentucky, on May 3, 1944. Dr. Simpson was born on May 11, 1875, in Jefferson County, Kentucky. He obtained his A.B. in 1908 from the University of Louisville, and M.D. in 1900 from the University of Louisville School of Medicine. Part of his earlier career was spent as a high school teacher. He joined the faculty of the University of Louisville School of Medicine as instructor in pharmacology and therapeutics in 1902; subsequently he became Associate Professor and Clinical Professor of Medicine.

For many years he was member of the staff of the Louisville City Hospital, the Norton Memorial Infirmary, the Kentucky Baptist Hospital, St. Joseph's Infirmary, Masonic Widows & Orphans Home, and Kosair Hospital for Crippled Children. He was a member of the Revision Committee of the U. S. Pharmacopoeia; Captain of the Medical Corps, Kentucky National Guard, 1909–16; service on the Mexican border, 1916–17; Major in the Medical Corps, U. S. Army, 1918–19, with overseas service as Commanding Officer of Company Hospital No. 8, Montigny le Roi, France.

A Diplomate, with special certification in gastroenterology, of the American Board of Internal Medicine; formerly, Secretary, Treasurer, and President, Jefferson County Medical Society; Member of the Kentucky State Medical Association, Southern Medical Association, American Heart Association, American Gastroenterological Association. For several years he served in the House of Delegates of the American Medical Association. He became a Fellow of the American College of Physicians in 1921, and rarely missed a College meeting, contributed to the ANNALS OF INTERNAL MEDICINE, as well as the annual meetings of the College, and was the author of many published papers.

Dr. Simpson was a man of very strong convictions. He was strongly opposed to the Murray-Wagner-Dingell Bill, and his death came suddenly after completing a vigorous address to the First District Nurses Association of Kentucky against the provisions of this Bill. As a teacher, diagnostician and clinician he enjoyed an enviable reputation. It is doubtful if in the entire Southland, and certainly not in Kentucky, one has worked so unselfishly, tirelessly, and unceasingly, and contributed more to organized medicine, than has Dr. Simpson. He will be sorely missed by his many patients, the Medical Department of the University of Louisville, and the Medical Profession of the entire South.

C. W. DOWDEN, M.D., F.A.C.P.,
Governor for Kentucky

DR. HUGH FRANCIS CRAWFORD

Dr. Hugh Francis Crawford died at his home in Memphis February 18, 1944. In his death the South has lost a physician who stood for the highest principles in our profession. He was highly intelligent, industrious and studious. He kept himself well informed in medical progress and used his knowledge to great advantage in the treatment of his patients.

Dr. Crawford was born in Williston, Tennessee, on June 16, 1882. He attended the Vanderbilt University for his academic work and the Memphis Medical College for his medical training. He devoted a lot of time to post-graduate work, spending most of his time at Tulane University.

He practiced medicine for twenty years in Wilson, Arkansas, and twenty years in Memphis where he limited his work strictly to Internal Medicine. He was not only one of our leading physicians, but also built up a fine reputation as a teacher. He was an Associate Professor at the University of Tennessee Medical School.

He has been a Fellow of the American College of Physicians since 1936; a Diplomate, American Board of Internal Medicine; member, Southern Medical Association, Tennessee State Medical Association, Memphis and Shelby County Medical Society and West Tennessee Medical Society; Fellow, American Medical Association.

WM. CALVERT CHANEY, M.D., F.A.C.P.,
Governor for Tennessee

DR. MICHAEL ALBERT ALBL

Dr. Michael Albert Albl (Associate), Cleveland, Ohio, died February 19, 1944, of pneumonia at the age of 74. He was born October 8, 1869, and after completing a preliminary education was graduated from Western Reserve University School of Medicine in 1892. Dr. Albl also was a graduate pharmacist.

He was extremely interested not only in medicine, but in the field of literature, and was a member of the Cleveland Library Association and Cleveland Clinical Club. He was a member of the Academy of Medicine, Fellow of the American Medical Association, and was an Associate of the American College of Physicians since 1925. He was a member of the Staff of St. Alexis Hospital.

A. B. BROWER, M.D., F.A.C.P.,
Governor for Ohio

DR. WILLIAM EDWARD NESBIT

William Edward Nesbit, M.D., F.A.C.P., of San Antonio, Texas, died on April 5, 1944, after an illness of only three days, of virus pneumonia. He was in his fifty-sixth year.

Dr. Nesbit graduated from Johns Hopkins University Medical School in 1913, and after serving as interne in hospitals in Roanoke, Virginia, and Baltimore, Maryland, he entered the Regular Army Medical Corps in 1917. Graduating from the Army Medical School, he went overseas with the Ninetieth Division in 1918, and was seriously wounded at St. Mihiel. At the end of the War, after his recovery, he settled in San Antonio, Texas, limiting his work exclusively to Internal Medicine. He was for many years Chief of Medical Service of the Robert B. Green Memorial Hospital. Besides being a member of the State, Southern, American Medical, and American Heart Associations, he was one of the organizers of the Texas Club of Internists, and since 1928 a Fellow of the American College of Physicians.

At the time of his death Dr. Nesbit was Chairman of the local Committee on Procurement and Assignment, Chairman of the Screening Committee of the Selective Service for more than two years, and devoted one-half of each day examining at the Induction Center, Dodd Field. A colleague has stated that "Dr. Nesbit was one of the honest and therefore one of the kindest and gentlest of men. Medicine to him was never a business and it was always more than a science. He cared for neither wealth nor fame, but loved his work because it furnished him with an opportunity to comfort and to help all those who suffer pain."

He is survived by his widow, Mrs. Fairfax Janin Nesbit, a daughter Fairfax Janin, and a sister Mrs. Zoie Nesbit Strother.

M. D. LEVY, M.D., F.A.C.P.,
Governor for Texas

DR. ROLAND N. KLEMMER

The sudden and untimely death of Dr. Roland N. Klemmer on May 9, 1944, has come as a shock to all who knew him. Dr. Klemmer had been on active duty with the Medical Corps of the United States Navy, as a Lieutenant Commander, since December 29, 1941, when he volunteered for service. At the time of his death, he was stationed in New Caledonia, where he had been in charge of the medical section of a naval mobile hospital.

Dr. Klemmer was born in Springfield, Massachusetts, in 1898. He received his A.B. degree in 1918 from Franklin and Marshall College, and was graduated in 1922 from the University of Pennsylvania School of Medicine. Dr. Klemmer later availed himself of postgraduate study in cardiology at the University of Pennsylvania Graduate School of Medicine and Harvard Medical School.

Shortly after receiving his medical degree, he became Pathologist at the Lancaster General Hospital, where he served for some years. Following this, he became Cardiologist and Chief of Staff at the Lancaster General Hospital, and from 1933 to 1938, Dr. Klemmer was Chief of Staff at the Lancaster County Hospital. Prior to going on active duty with the Navy, he resided in Lancaster, Pennsylvania.

Dr. Klemmer was a member of the Lancaster County Medical Society, Pennsylvania State Medical Association and American Medical Association. He was a Fellow of The American College of Physicians since 1930, and was likewise a Diplomate of the National Board of Medical Examiners and American Board of Internal Medicine.

In addition to the personal loss to his fellow associates and friends, medicine has lost one of its most capable students and staunch supporters. Dr. Klemmer was an inspiring leader in the medical profession, and his passing is acknowledged with humble tribute.

EDWARD L. BORTZ, M.D., F.A.C.P.,
Governor for Eastern Pennsylvania

DR. JACOB EARL MEENGS

Dr. Jacob Earl Meengs, F.A.C.P., died February 2, 1944, of valvular heart disease, arteriosclerosis and general edema with pleuritic effusion on the right side.

Dr. Meengs was born in Holland, Michigan, August 4, 1881, and received his M.D. at Rush Medical College in 1904. He was Resident Physician in Lennox Hill Hospital, New York City, from 1911 to 1913, and did postgraduate work in 1913 and 1914 at the Victoria Augusta Hospital, Berlin, Germany, and at the Allgemeine Krankenhaus, Vienna, Austria. He was a member of Kent County Medical Society and Michigan State Medical Society; Fellow of the American Medical Association and of the American College of Physicians; Diplomate, American Board of Internal Medicine.

Dr. Meengs was not known to the writer, but I am advised by those of his colleagues who knew him best that he was a quiet, reserved, studious man, slow to take up new methods, but respected by his fellow practitioners and the public.

P. L. LEDWIDGE, M.D., F.A.C.P.,
Acting Governor for Michigan

DR. FRANK BOLLES WAKEMAN

Colonel Frank Bolles Wakeman, who was a Fellow of the American College of Physicians, died March 17, 1944, at Fort Monmouth, New Jersey, of a coronary occlusion.

Colonel Wakeman was born at Sidney, New York, on May 15, 1896. He graduated in pharmacy from Valparaiso University in 1915, received his degree in pharmaceutical chemistry in 1916 and a B.S. in chemistry from the same school in 1917. From August 1917 to May 31, 1919, he served as first lieutenant, infantry, Officers Reserve Corps, going overseas with the 369th U. S. Infantry. After several years spent in the educational field, part of the time as a high school principal, he matriculated at the Indiana University School of Medicine, where he received his M.D. in 1926. After

graduation and the completion of an internship at Walter Reed General Hospital, he practiced medicine in Indiana until 1928 when he was appointed a first lieutenant in the Medical Corps, Regular Army. He was promoted to captain, U. S. A., on June 3, 1928, major, U.S.A., on June 4, 1937, lieutenant colonel, A.U.S., on February 1, 1942, and colonel, A.U.S., on September 8, 1942.

During his Army career Colonel Wakeman continued his scientific studies, receiving the degree of Master of Arts from Catholic University of America in 1933 and the degree of Doctor of Philosophy from the same institution in 1935. In 1937 he earned the degree of Doctor of Public Health from Johns Hopkins School of Public Health. Service courses which he completed were the basic course, Army Medical School, in 1929, and the advanced course, Army Medical School, in 1936; the basic course, Medical Field Service School, Carlisle Barracks, in 1929, and the advanced course at the same school in 1938; and the Command and General Staff School, Fort Leavenworth, Kansas, in 1940. Teaching assignments during this period included a tour as instructor in biochemistry at the Army Medical School from 1932–1936, and a tour as instructor in sanitation at the Medical Field Service School from 1937–1939. In 1938 he was awarded the Henry Wellcome prize by the Association of Military Surgeons of the United States for his essay on "A Specific Somatic Polysaccharide as the Essential Immunizing Antigen of the Typhoid Bacillus."

In February 1940 Colonel Wakeman was assigned to the Training Division, Surgeon General's Office, and became its director in July of the same year. While serving in that capacity Colonel Wakeman laid the plans and was more responsible than any other man for the execution of the vast training program of the Medical Department during the current emergency and war. It is indeed fortunate that a man of such foresight, organizing ability, and energy was available to the Medical Department during this period.

NORMAN T. KIRK, Major General, U.S.A.,
A.C.P. Governor

DR. JACOB GUTMAN

Dr. Jacob Gutman, F.A.C.P., Brooklyn, New York, died in the Presbyterian Hospital, May 7, 1944, following a short illness. He was born in Riga, Latvia, June 22, 1876; attended the Alexandre Gymnasium and the School of Catherine the Great, Riga; M.D., 1900, Cornell University Medical School; Phar.D., 1914, University State of New Jersey; for many years, Medical Director of the Brooklyn Diagnostic Institute; Consulting Physician, Manhattan General (New York City), Shore Road, Boro Park General, Riverdale and Williamsburgh Maternity Hospitals; Chief Medical Diagnostician and Honorary Surgeon, New York City Police Department.

Dr. Gutman was a member of his county and state medical societies, American Medical Association, American Therapeutic Society, American Congress of Physical Therapy, American Medical Editors and Authors Association, Williamsburgh Medical Society, East New York Medical Society and others. He had been a Fellow of the American College of Physicians since 1920. He was the author of many published papers, and of "Modern Drug Encyclopedia and Therapeutic Guide."

ASA L. LINCOLN, M.D., F.A.C.P.,
Governor for Eastern New York

DR. HARRY J. BELL

Dr. Harry J. Bell, F.A.C.P., Dawson, Pa., died September 30, 1943, aged 76. Dr. Bell was born at Arendtsville, Adams County, Pa., in 1868. He attended the public schools and spent one year in the preparatory department at Muhlenberg College. He received his Medical Degree from the Medico-Chirurgical College of Philadelphia in 1892. For many years, he had been on the staff of the Connellsville State Hospital. He was a member of the Fayette County Medical Society, Pennsylvania State Medical Society, American Medical Association, and had been a Fellow of the American College of Physicians since 1924.